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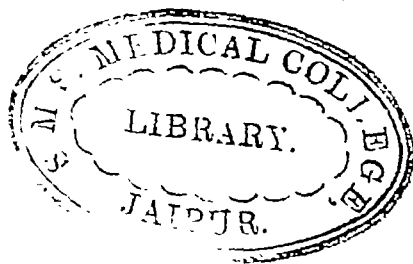
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# CONTENTS

	PAGE
<b>SYMPOSIUM ON FEVERS OF OBSCURE ORIGIN IN CHILDHOOD</b>	1
<b>Introduction.</b>	3
By DR. JOSEPH STOKES, JR.	
<b>Fever Due to Upper Respiratory Infections</b>	9
By DR. MITCHELL I. RUBIN	
<b>Fever Due to Lower Respiratory Infections</b>	17
By DR. CHARLES C. CHAPPLE	
<b>Fever of Abdominal Origin</b>	21
By DR. JOHN MCKENNEY MITCHELL	
<b>Fever Due to Diseases of the Urinary Tract</b>	31
By DR. MITCHELL I. RUBIN	
<b>Fever Discussed from the Standpoint of Central Nervous System Disease</b>	35
By DR. T. S. WILDER	
<b>Fever Due to Miscellaneous Conditions</b>	47
By DR. CHARLES C. CHAPPLE	
<b>SYMPOSIUM ON COMMON OBSTETRIC AND GYNCOLOGIC PROBLEMS OF THE FAMILY PHYSICIAN</b>	59
<b>Sterility</b>	61
By DRS. P. BROOKE BLAND and ARTHUR FIRST	
<b>Diagnostic Mistakes in Gynecology</b>	75
By DR. NORRIS W. VAUX	
<b>The Causes of Abnormal Vaginal Bleeding During the Pre- and Postmenopausal Ages</b>	83
By DR. FRANKLIN L. PAYNE	
<b>Treatment of Habitual Abortion</b>	93
By DR. MARGARET CASTEX STURGIS	
<b>The Diagnosis and Treatment of Cyanosis of the Newborn</b>	99
By DR. AARON CAPPER	
<b>Treatment of Chronic Endocervicitis and Vulvovaginitis</b>	119
By DR. THOMAS J. COSTELLO	
<b>Notes in the Field of Geriatrics</b>	127
By DR. O. H. PERRY PEPPER	
<b>The Treatment of the Complications of Gonorrhea in the Male</b>	147
By DR. P. S. PELOUZE	
<b>The Management of Chronic Prostatitis</b>	161
By DR. FREDERICK S. SCHOFIELD	
<b>The Diagnosis and Treatment of the More Common Cardiac Arrhythmias</b>	175
By DR. HENRY K. MOHLER	
<b>Physical Exercise in Cardiac Conditions</b>	191
By DR. JOSEF B. NYLIN	
<b>Preventive Aspects of Cardiovascular-Renal Disease</b>	209
By DR. CHARLES L. BROWN	
<b>Incipient Parkinsonism: Diagnosis and Treatment</b>	223
By DR. A. M. ORNSTEEN	
<b>The Treatment of Herpes Zoster</b>	239
By DRS. DONALD M. PILLSBURY and GEORGE H. FONDÉ	
<b>Genetic Aspects of Certain Blood-system Disorders</b>	253
By DR. THOMAS FITZ-HUGH, JR.	
<b>Botulism—a Report of Two Suspected Cases</b>	265
By DRS. GARFIELD G. DUNCAN and O. NORRIS SMITH	
<b>Diabetes Mellitus and Hypothyroidism with a Report of a Case</b>	279
By DR. JOHN DURKIN	
<b>Hyperthyroidism: An Evaluation of Blood Iodine, Impedance Angle and Basal Metabolic Rate in Borderline Cases</b>	285
By DR. MICHAEL G. WOHL	
<b>Diagnosis of Diseases Associated with Enlargement of the Liver or Spleen</b>	295
By DR. BERNARD I. CONROE	
<b>Scarlet Fever Today</b>	307
By DR. EDWARD L. BAUER	
<b>Treatment of Acute Pleurisy in General Practice</b>	323
By DR. MARTIN J. SOKOLOFF	
<b>Cumulative Index</b>	331

*Philadelphia Number*

# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON FEVERS OF OBSCURE ORIGIN IN. CHILDHOOD

The following clinics are included in this Symposium:

Joseph Stokes, Jr.: INTRODUCTION.

Mitchell I. Rubin: FEVERS DUE TO UPPER RESPIRATORY INFECTIONS.

Charles C. Chapple: FEVERS DUE TO LOWER RESPIRATORY INFECTIONS.

John McKenney Mitchell: FEVERS OF ABDOMINAL ORIGIN.

Mitchell I. Rubin: FEVERS DUE TO DISEASES OF THE URINARY TRACT.

T. S. Wilder: FEVERS DISCUSSED FROM THE STANDPOINT OF CENTRAL NERVOUS  
SYSTEM DISEASE.

Charles C. Chapple: FEVERS DUE TO MISCELLANEOUS CONDITIONS.



## SYMPOSIUM ON FEVERS OF OBSCURE ORIGIN IN CHILDHOOD

### INTRODUCTION

JOSEPH STOKES, JR.

EVERY practitioner of medicine is faced many times yearly with a puzzling infant or child who shows day after day an elevation of temperature of obscure origin. Each morning the physician's hopes may rise as the parents report a temperature approaching normal, and each evening they are dashed again as the eyes of the parents search his face for any sign of hope or recognition of the cause.

Professional reputation and the regard of a community for the practitioner depend more upon the management of such cases than upon almost any other phase of medical practice.

Equally puzzling, but ordinarily not as momentous for professional reputation, are the obscure fevers of short duration, one, two, or three days, which frequently rise to alarming heights with great rapidity, and then as rapidly drop toward a normal figure. It is perhaps in this latter group of short duration more than in the former, that the child frequently is "cured" without a rational explanation for either the fever or the "cure." For the parent the rapid "cure" is usually sufficient evidence to quiet whatever doubts he may have had concerning the practitioner's guarded explanations of the cause.

Driven more by the apparent necessity of presenting some valid explanation to the parents rather than to himself the practitioner will often announce the diagnosis without mentioning alternatives, which he fears the parents may regard

as lack of knowledge. In such a position he may feel the necessity of bolstering and confirming from day to day his original diagnosis, which is possibly incorrect, and in this way he not only becomes less alert, but even shuts his mind to the correct diagnosis, or to the facts which may lead to a correct diagnosis. This type of intellectual dishonesty is readily acquired and too often practiced inasmuch as parents, usually ignorant of medical facts, appear to be more readily satisfied and relieved by a single definite diagnosis announced with considerable confidence.

Certainly when the origin of the fever is obscure the primary emphasis to the parents should be placed upon the importance of continued thorough investigation by all laboratory and clinical means available. Emphasis also upon the more probable causes is obviously essential, but the parents should never be unaware of the physician's lack of complete certainty.

It is the observation of keen practitioners who have had long and valuable experience that one of the most frequent, if not the most frequent, difficulty in the diagnosis of fevers of obscure origin is not the lack of a careful examination, nor the failure to analyze carefully signs and symptoms, but the fact that the correct cause of the condition does not happen to occur to them. At times the occurrence of the fortunate thought almost appears to be a matter of mere chance. And yet it is well recognized that the practitioner who has had excellent training in pathology at the beginning of his career and who continues to frequent the mortuary is far more apt to keep in mind the variety of diagnoses that must always be carefully reviewed under such circumstances. In the diagnosis of fevers of obscure origin an intimate acquaintance with pathological variations in the body organs is often of greater importance than the examination of the patient, however important the latter may be.

The objectives then of this symposium are essentially the following:

1. To present in reasonable order the names of a variety of diagnoses which might not readily occur to every practi-

tioner having difficult diagnostic problems in which fever of obscure origin is the outstanding feature.

2. To review under each diagnosis or group of diagnoses a few facts of outstanding clinical importance.

## INDEX OF DIAGNOSES

### FEVERS DUE TO UPPER RESPIRATORY INFECTIONS

1. The common cold.
2. Tonsil and adenoid infection.
3. Paranasal sinus infection.
4. Retropharyngeal abscess.
5. Cervical lymphadenitis.
6. Otitis media and mastoiditis.

### FEVERS DUE TO LOWER RESPIRATORY INFECTIONS

1. Pneumonia.
2. Influenza.
3. Diaphragmatic pleurisy.
4. Encapsulated empyema.
5. Multiple lung abscess.
6. Bronchiectasis.
7. Mediastinal glands.
8. Mediastinal Hodgkin's disease.
9. Mediastinal abscess.
10. Tuberculosis.

### FEVERS OF ABDOMINAL ORIGIN

Cases in which fever is of long duration and of variable degree:

Abdominal tuberculosis:

1. Intestinal tuberculosis.
2. Tuberculous peritonitis.
3. Tuberculosis of the mesenteric lymph nodes.

Cases of acute febrile illness in which fever is a predominant symptom and in which signs point only indefinitely to the abdomen:

1. Typhoid fever and paratyphoid fever.
2. Bacillary dysentery.
3. Amebic dysentery.
4. Ulcerative colitis.

Cases with abrupt onset and symptoms point to an acute surgical abdomen:

1. Acute appendicitis.
2. Chronic appendicitis.
3. Peritonitis.
4. Primary pneumococcal or streptococcal peritonitis.



5. Abscesses in the abdominal region.
6. Subphrenic abscess and liver abscess.
7. Acute pancreatitis.

#### FEVERS DUE TO DISEASES OF THE URINARY TRACT

1. Pyuria (pyelitis).
2. Carbuncle or multiple abscesses of the kidney.
3. Perinephric abscess.
4. Tuberculosis of the kidney.
5. Cystitis.
6. Urinary calculi.
7. Neoplasms.

#### FEVERS DISCUSSED FROM THE STANDPOINT OF CENTRAL NERVOUS SYSTEM DISEASE

1. Meningococcic meningitis.
2. Tuberculous meningitis.
3. Meningitis due to streptococcus, staphylococcus, pneumococcus, Pfeiffer's bacillus, colon bacillus, and other common organisms.
4. Poliomyelitis.
5. Encephalitis.
6. Acute lymphocytic meningitis.
7. Acute lymphocytic chorio-meningo-encephalitis.
8. Syphilitic meningitis.
9. Brain abscess.
10. Pachymeningitis.
11. Mechanical factors.
12. Toxic drugs.
13. Miscellaneous conditions apparently acting directly on the brain.

#### FEVERS DUE TO MISCELLANEOUS CONDITIONS

##### Diseases of the newborn:

1. Dehydration fever.
2. Sepsis of the newborn.

##### Diseases of infancy:

1. Teething.
2. Roseola infantum.
3. Scurvy.

##### Acute diseases with joint involvement:

1. Osteomyelitis.
2. Rheumatic fever.

##### Diseases chiefly involving the blood.

1. Leukemia.
2. Acute infectious mononucleosis.
3. Purpura.

## INTRODUCTION

7

4. Subacute bacterial endocarditis.

5. Sickle cell anemia.

### Chronic diseases:

1. Malaria.

2. Hodgkin's disease.

3. Undulant fever.

### Infections due to animal contact:

1. Psittacosis.

2. Tularemia.

### The more unusual diseases:

1. Rocky Mountain spotted fever.

2. Typhus.

3. Rat-bite fever.

4. Relapsing fever.

### Miscellaneous causes:

1. Mechanical prevention of evaporation.

2. Abscessed teeth.



## FEVERS DUE TO UPPER RESPIRATORY INFECTIONS

MITCHELL I. RUBIN

By far the commonest cause of obscure fever in childhood is infection in the upper respiratory tract. The "obscurity" of the fever is usually of short duration, for repeated careful examinations over a period of time most often throw light upon the etiological factors.

1. **The Common Cold.**—It has been facetiously said that the doctor who could not at least find an infected throat to account for the fever is a poor physician, yet many an attack of obscure fever goes undiagnosed simply because the physician fails to examine the throat of the child. Frequently one is called into the out-patient clinic to help in the diagnosis of a child presenting an obscure fever where the cause lay in an infected throat which was not examined. While it is true that the examination of the throat in an infant or child may be difficult due to the accumulation of secretion or to the perverseness of the patient, yet certainly the vast majority of brief febrile bouts in this age group are due to infections in the nasopharynx. Often for twenty-four to thirty-six hours after the onset of fever in cases of so-called "colds" the only inflammation of the mucous membrane in the upper respiratory passages that may be demonstrated occurs in the nose and conjunctivae. At this stage the pharynx not infrequently appears normal. It seems wise that the examination of the upper respiratory tract in children should include the study of the nose with electrically lighted nasal speculum. The large size speculum of the usual otoscopic set is useful for this purpose. Attacks of prolonged obscure fevers in childhood most frequently result from or are continuations of this so-called "simple cold."

2. **Tonsil and Adenoid Infection.**—The frequency with which a residual tonsillar infection is the basis for prolonged obscure fever is problematical. Certainly there are many instances of this, but just as assuredly, there are many more where the tonsils are held at fault and where tonsillectomy is performed without relief.

How and when can we consider the tonsils as the cause of the unexplained fever when examination fails to find some other etiological factor? How can chronic disease of the tonsils be recognized?

While growth of lymphoid tissue is dependent upon individual and familial variation and upon the state of nutrition (the well-nourished children having larger lymphoid structures than those undernourished), it is generally held that chronic infection of the tonsils, adenoids, or other lymphoid structures in the nasopharynx produces hypertrophy. Certainly not all enlarged tonsils or adenoids are chronically infected, and again, chronic infection may exist in these structures when they appear small. The small buried and scarred tonsil has often proved to be the focus of infection which was producing a low-grade fever. More important than the size of the tonsil alone in making one suspicious of chronic infection here is the history of repeated "sore throats" and other associated pathological findings. Palpation of the tonsil has been recommended to determine the amount of adhesions and the degree of burying. However, this is not a very satisfactory procedure. The presence of chronically reddened anterior pillars and more especially chronic enlargement of the cervical lymph nodes is indicative of tonsillar infection. Enlargement of the so-called "tonsillar node" which is situated just below the angle of the jaw is of great diagnostic importance in indicating chronically diseased tonsils. Cultures taken from the tonsillar surface have not proved of value in determining chronic infection of this organ. Some clinicians feel that when the tonsil surface is smooth and the normal crypts are not seen that chronic infection in the tonsil is most likely. Remote disease such as rheumatic infections and nephritis are said to be indications of an

infection in the tonsils, or in some other area of the upper respiratory passages. Chronic infection of the tonsils in most instances is not associated with continued pyrexia but often it does produce a low-grade intermittent fever. The degree of fever produced will vary with the individual child. Some children have a more stable temperature regulation than others. The neurotic, highly emotional child will respond to simple infections with much more fever than would the more phlegmatic child. It is to be remembered that the daily fluctuations of the normal body temperature are between  $1^{\circ}$  and  $1\frac{1}{2}^{\circ}$  F. The emotional child without any infection whatsoever, may have a wider daily fluctuation in body temperature, anywhere from  $1^{\circ}$  to  $2^{\circ}$  F. The fluctuations in the temperature curve occur above and below the normal base line of  $98.6^{\circ}$  F.

Whether chronic infection of the adenoids alone will produce continued fever is not clear. Infection of these structures is most often associated with infection of the tonsils or result from infection of the sinuses which by producing a postnasal "drip" infects the adenoids.

There occurs not infrequently, especially in children where tonsillectomy and adenoidectomy have been performed early in life, some hypertrophy of the lymphoid tissue on the post-pharyngeal wall. These nodules of lymphoid tissue often become infected directly or as a result of a postnasal drip from infected sinuses. Small ulcerations appear in these lymphoid nodules and remain for long periods. Dr. Edward H. Campbell, the Otolaryngologist to the Children's Hospital, is of the opinion that this type of lymphoid infection can produce a prolonged low-grade fever which will subside after removal of this tissue. He believes that this infected tissue is best removed by electrocoagulation.

**3. Paranasal Sinus Infection.**—Probably the second commonest cause of low-grade obscure fever in children is paranasal sinusitis. At early age periods infection of certain of the sinuses need not be considered. The time of their development, however, is quite irregular. The ethmoid sinuses are well developed at birth and as a result of this early develop-

ment they are commonly the seat of infection early in infancy. The maxillary sinus which is probably the second most commonly infected sinus is present at birth but develops a little later than does the ethmoid sinus. The frontal sinuses and the sphenoidal sinuses are rarely infected before the seventh year of life. During each attack of a so-called "cold" there must be some involvement of the paranasal sinus which clears when the "cold" subsides.

It has been more recently demonstrated that the etiological agent in inciting a "cold" is a filtrable virus. It has also been suggested that the more severe symptoms resulting from a simple "cold" are due to certain pathogenic bacteria which become active due to the presence of the virus. It is these secondarily invading bacteria which ultimately produce chronic infection in the sinuses following one or more colds, or one of the acute exanthemata. Once the sinuses become infected they only slowly clear up. During the acute phase of sinusitis the cause of the resulting fever is rarely obscure. There is usually in this phase of the disease a profuse nasal discharge appearing anteriorly or as a postnasal drip. It may be unilateral but is most often bilateral. There is almost always an associated rhinitis. If the opening to the sinus is blocked, the symptoms are more acute. Tenderness and edema over the involved sinus are usually seen in the acute phase only, and then not always. When the ethmoids are involved edema and redness appear at the inner side of the eye and base of the nose. Both the upper and lower lids may become involved. Older children complain of pain over the involved sinus. The fever during this acute phase is not unlike that seen in acute tonsillitis, subsiding after a few days. If the acute infection fails to clear or if repeated acute attacks occur a chronic sinusitis develops, often with a low-grade fever accompanying it. As with chronic tonsillitis, fever is usually not a symptom of chronic sinusitis. The younger the child the more likely is he to have fever with this condition, and the less acute the process the lower is the febrile response. The temperature curve usually shows daily afternoon fluctuations up to

100° or 100.5° F. rectally. This may persist for weeks or longer, especially during the winter months when frequent mild exacerbations are occurring.

After all *other possible causes for the fever* have been exhausted without avail, the sinuses should be carefully investigated, more especially if there is a history of frequent "colds." The physical signs mentioned as occurring during the acute stage are usually not seen here. The x-ray in older children has been of great help in localizing the infection, but in younger children it has not been so helpful. It has been claimed that (by demonstration through x-ray examination) if retardation in the normal sinus development has occurred, one can assume that chronic infection in the sinuses exists. However, because of the normal irregular development of the sinus this would be of value only in the long standing cases. The most accurate diagnosis is made by a careful nasopharyngoscopic examination performed by a rhinolaryngologist. Transillumination in the young child is unsatisfactory. Often the diagnosis can only be made by sinus puncture with the release of pus. The postnasal drip of mucopus so often seen, in most instances arises from infection in the sinuses. It is the opinion of the rhinolaryngologists in the clinic of the Children's Hospital that the adenoids rarely produce any of this postnasal drip. A unilateral optic neuritis or local disease of the bone or eye has often been the clue to a hidden sinus infection.

A unilateral nasal infection due to a foreign body or some other local disease may be a cause of an obscure fever.

4. **Retropharyngeal Abscess.**—We have seen many cases of prolonged unexplained fever where ultimately a retropharyngeal abscess proved to be the cause. When the abscess is so situated or is of such size as to produce respiratory obstruction or difficult swallowing the diagnosis is not obscure. When the swelling does not produce these signs the diagnosis is not so obvious. The origin of this abscess is in the retropharyngeal lymph nodes. At times the infection in the node does not proceed on to suppuration and remains as a retropharyngeal lymphadenitis, later subsiding with a disappear-



ance of the mass. Suppuration may take place, progressing until the entire retropharyngeal space is one large abscess, even burrowing down into the mediastinum. The smaller the mass the fewer the symptoms. Usually the mass is to one side of the median line. When the nodes high up in the retropharynx are involved, nasal obstruction alone is present. When the nodal involvement is lower, swallowing is interfered with and the child gurgles his saliva. When the larynx is compressed respiratory distress is obvious. All cases of stridor should be investigated for the presence of a retropharyngeal abscess. Another striking sign is marked localized cervical gland enlargement occurring in the region of the "tonsillar" node. Often this mass presents a deep fluctuation. However, when this latter sign is present the fever is not obscure. Most retropharyngeal abscesses occur under three years of age. Those due to cervical Pott's disease present their swellings in the median line.  $\alpha$ -Ray examination is of great help in demonstrating a retropharyngeal swelling (the trachea bulges forward) or bone disease where present. In the smaller retropharyngeal abscesses, unless this condition is suspected as a cause of low grade fever it is often undiagnosed. Digital examination is the most reliable diagnostic procedure. Care should be exercised not to open the child's mouth too widely or depress the tongue too forcefully during the examination since we have seen several cases of sudden asphyxia from this.

**5. Cervical Lymphadenitis.**—When acute cervical lymphadenitis exists the cause for the fever is not obscure. This condition is mentioned here only because not infrequently there is a failure to appreciate the disturbance and amount of fever which acute adenitis may cause in children. The acute adenitis is almost always secondary to acute infections in the nasopharynx. However, not infrequently the primary infection has long since subsided and there remains only the telltale lymphadenitis. Even though suppuration does not develop, fever may persist for weeks or months as long as the glands remain enlarged. This prolonged fever often results in

many consultations where each clinician after careful study is forced to conclude that the only cause for the persistent fever is the adenitis.

The temperature which is usually remittent may be slight or may vary several degrees. In young children stiffness of the neck or torticollis may result as a protection to prevent irritation of a deep seated infected lymph node. The younger the child the more likely is the gland to suppurate.

**6. Otitis Media and Mastoiditis.**—Rarely is otitis media a cause of obscure fever if a thorough examination is made. However, from a practical standpoint it is often a cause of unexplained fever simply because the ear has not been properly examined. Save by those most expert an electrically lighted otoscope should be used. In cleaning the ear care should be taken that the drum itself is not injured, for then mild cases might be entirely overlooked or incorrectly diagnosed. In the young infant, crying produces some pinkness of the drum but the other signs will not indicate otitis.

The usual acute mastoiditis is obvious. Only in the so-called "hidden" types or when the infection extends into the petrous portion of the temporal bone rather than externally does the diagnosis and the cause of the fever become obscure. The so-called "hidden" mastoid is the type seen in young marantic infants. There is usually a discharging ear with no local signs over the mastoid area. A sagging of the posterior superior canal wall may be observed. Since some infection of the antrum is always seen in middle ear infections it is difficult to know what constitutes a definite so-called "mastoid (antrum) involvement." A posterior antrotomy performed on these patients often produces no change in the constitutional or febrile course of the patient.

In those cases where a petrous abscess develops the diagnosis is often obscure. Only when the abscess extends to the dural surface and produces a typical syndrome such as the "Gradenigo syndrome" is the diagnosis suspected.

However with this type of mastoid infection, as is usual in almost all mastoid infections, there is an associated otitis

media. Thus, when the temperature curve is at all out of the way for the simple case of otitis media, mastoid involvement should be suspected.

In those cases where an infected lymph node overlies the mastoid and where an otitis media exists it may prove very difficult to say whether or not mastoiditis exists. Such cases often require a period of observation before a conclusion can be reached.

## FEVERS DUE TO LOWER RESPIRATORY INFECTIONS

CHARLES C. CHAPPLE

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BEFORE considering lower respiratory infections it is well to have a few facts in mind. First, children under six years of age do not expectorate. When sputum is present it is swallowed or aspirated. Its absence from the bedside container does not mean its absence from the child. Second, the respiratory rate normally falls from 35 to 50 a minute in the newborn to 30 per minute for the remainder of the first year. After this period it gradually diminishes to 20 to 25 per minute for the rest of childhood and reaches the adult rate at puberty. With fever the respiratory rate is increased approximately  $2\frac{1}{2}$  respirations per degree of elevation. A respiratory rate over 40 per minute warrants a tentative diagnosis of respiratory tract infection until it can be excluded.

**Pneumonia.**—Seldom indeed can pneumonia be safely discarded from the diagnostic possibilities in sudden, high fevers. Definite clinical evidence of its presence is frequently delayed and may not appear until the crisis. Abdominal pains and a rigid abdominal wall may be most misleading and extremely difficult of differentiation from an acute abdominal condition. x-Ray examination cannot be depended upon to give conclusive evidence against pneumonia's presence in the early stage of the disease. Fluoroscopy may be of value in the demonstration of limitation of diaphragmatic motion when an abdominal diagnosis must be ruled out. The white blood count tends to reach a much higher point in pneumonia than in acute abdominal disorders. But after all close clinical observation has no substitute as a diagnostic procedure.

**Influenza.**—The difficulty obtaining in the diagnosis of this disease is one of quite another order. This diagnosis is commonly used as a camouflage answer for all problems of obscure solution. A leukopenia of 6000 or below is a necessary concomitant of the fever, respiratory or gastro-intestinal signs when their cause is influenzal. Pfeiffer's bacillus can frequently be recovered from the throat and nose but is not at all diagnostic.

**Diaphragmatic Pleurisy.**—Signs on auscultation and percussion may be lacking in pleurisy especially when it is located exclusively on the diaphragm. Hiccough and abdominal pain may serve to fasten a diagnosis upon a pleuritic picture which offers no evidence to the stethoscope.

**Encapsulated Empyema.**—When a child fails to blossom after a pneumonia and the temperature persists though the chest sound clear, this condition is a first rank possibility. x-Ray plates will disclose the interlobar collection.

**Multiple Lung Abscess.**—When the individual abscesses are small, though they be myriad, there will be no sign demonstrable to auscultation or percussion. The clinical picture is one of great severity in other particulars. Chills, high fever, foul breath, cough, and expectoration are usual. Pallor, cyanosis, nausea, pleuritic pain and finger clubbing commonly accompany this condition. Dark-field examination of the sputum for spirochetes and fusiform bacilli should be performed. Smears and cultures of the expectorated matter must be examined for their presence. Roentgenograms will shortly give corroboration.

**Bronchiectasis.**—Fever recurs at irregular intervals in this condition but the x-ray plates of the chest, especially those taken after lipiodol injection, are diagnostic so that this disease can hardly be classified as of obscure origin.

**Mediastinal Glands.**—A persistent fever following an upper respiratory tract infection may be due to mediastinal gland involvement. Cough of a brassy type is frequently present here. The respiratory rate may be slower than that ex-

pected. Critical x-ray examination leads to the solution of this diagnostic problem.

**Mediastinal Hodgkin's Disease.**—Hodgkin's is described elsewhere.

**Mediastinal Abscess.**—A clue to the origin of this disturbance is usually to be found in the immediate past history of the child revealing a cervical or throat infection. The onset is one of great severity. Chills, high fever, and dyspnea are present. He sweats profusely and may complain of back-ache. A blood culture should be done immediately. The white blood count will be greatly elevated with a preponderance of polymorphonuclears. If the abscess be of appreciable size it will be demonstrable by x-ray.

**Respiratory Tuberculosis.**—Childhood tuberculosis presents quite a different picture from that seen in older persons. It is a primary disease in the child and secondary in the adult. This distinction is based upon the presence of tissue reactivity due to previous infection in the adult. It is analogous to, if not identical with, allergy. The child, receiving his first infection has not set up such responses of defense that he can confine the organisms to a small area. The primary site in the lung is the origin of lymphangitis between itself and the regional lymph nodes where a lymphadenitis is established. These three processes together are known as the primary triad. The adult walls off the organism at point of entry in the lung without the extensive lymphatic involvement characteristic of childhood tuberculosis. Childhood tuberculosis can occur in the adult who has had no previous exposure to the disease as can the adult type appear in the child with an earlier contact.

Once tuberculosis is established the symptoms and signs can be legion. Continuous low-grade fever, cough, night sweats, pallor, loss of appetite and secondary anemia are almost constantly present. The location of the tubercles determines the characteristics of other signs. These may be gastro-intestinal, genito-urinary, muscular, neurological, or

skeletal in type. Deafness, hoarseness, dimness of vision may be present. The variations are limitless.

x-Ray examination of the chest will reveal enlarged mediastinal glands and the primary site which is often found to be calcified. Old tuberculin injected intradermally will produce an area of redness at the point of inoculation in case either of present activity or past infection. The first skin test dose is  $\frac{1}{100}$  mg. but this should be increased to 1 mg. if smaller doses be negative. A positive skin test is not to be understood as excluding all other causes of fever. Positive tests occur more and more frequently as the child grows older so that few adults have negative tests. The severity of the skin test reaction must be taken into consideration as well as all possible diagnostic means for the determination of other causes. It should be remembered that the skin test can be negative although tuberculosis be actively present. This is true after measles, for example, and in overwhelming miliary and meningitic forms of the disease.

## FEVERS OF ABDOMINAL ORIGIN

JOHN MCKENNEY MITCHELL

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### CASES IN WHICH FEVER IS OF LONG DURATION AND VARIABLE DEGREE

ABDOMINAL tuberculosis must be granted a position of first importance in any search for the origin of fever in a child in whom the duration of such fever has been prolonged and where other symptoms may point even indefinitely to the abdomen. Tuberculous lesions of the intestines, peritoneum and mesenteric lymph nodes, although decreasing at a faster rate than those of the pulmonary region, remain a common site of tuberculosis in young children. They are found in a high percentage of autopsies on tuberculous children, in approximately 10 per cent of which they represent the oldest lesion.

Abdominal tuberculosis is most frequently primary, infection occurring through the intestines from infected food. A history of the habitual or periodic use of raw milk from untested or infrequently tested herds is obtainable in a large percentage of cases, and the incidence is decidedly lower in the cities than in rural and semirural areas where there is less rigid milk control and less pasteurization. Ice cream, "our own make," often from milk of uncertain origin is doubtless the source of others. A smaller number of cases are secondary to pulmonary tuberculosis, being derived from sputum which is coughed up and swallowed.

Intestinal tuberculosis presents symptoms of great irregularity. In the milder cases localizing manifestations are usually entirely absent, and the condition must be suspected



on the basis of the constitutional reaction, in which low-grade fever of unexplained origin is the most common factor. This may or may not be accompanied by loss of weight or failure to gain, anorexia, anemia, and fatigability. In the more advanced cases there is often diarrhea of an obstinate sort, and occult blood. Gross hemorrhages are not common.

**Tuberculous peritonitis** is associated with many of these advanced intestinal lesions in which case symptoms of low-grade peritoneal involvement are present. Abdominal pain and tenderness may however be absent. There is almost always some fever, 100° to 101° F., though even this may not develop early. A slowly developing ascites is the most common finding. In the plastic forms which develop more slowly and insidiously, fever is slight and often absent. As the condition advances fever appears and reaches higher levels. Tuberculous peritonitis may occur in cases in which intestinal tuberculosis is not discovered, it having been amply demonstrated that the infection may pass through the intestinal wall and leave no trace.

Cirrhosis of the liver is not infrequently confused with tuberculous peritonitis. Since this condition also often shows an evening rise of temperature, the presence of fever is of little diagnostic help.

In acute miliary tuberculosis blood-borne infection may leave tubercles scattered over the peritoneum and give no local signs. Fever is a prominent symptom.

**Tuberculosis of the mesenteric lymph nodes** is associated with tuberculosis of the intestines and peritoneum in the vast majority of instances and is frequently the only demonstrable lesion clinically or at autopsy. Such glands vary greatly in size, fusion sometimes resulting in palpable masses. They may be relatively symptomless but often produce fever, pain, local tenderness and rigidity, sometimes so great as to be confused with appendicitis. They are found somewhat more commonly (60 per cent) on the right side, and above McBurney's point, corresponding anatomically to the glands of the ileocecal mesentery. As active infection subsides and calcifica-

tion of the glands occurs, recurrent attacks of abdominal pain continue in about one half of the cases, in some instances over a period of years. In this stage fever is less apt to be present, usually only during the attacks of pain, and is of low grade (100° F.). Such glands are demonstrable roentgenologically and have been found to be present in from 1 to 2 per cent of abdominal plates of children between two and twelve years of age.

A positive tuberculin test is always present in abdominal tuberculosis and in the young child is the mainstay of the diagnosis. After calcification lesions of the mesenteric lymph nodes are readily demonstrable by flat x-ray plates of the abdomen and render possible a clear-cut diagnosis of this most common form, even when asymptomatic.

Rest, heliotherapy and attention to hygiene and diet with especial attention to removal of the source of infection when this is milk, are usually sufficient to eventually result in a cure. Surgical intervention with excision of involved glands should be reserved for those cases who fail to respond to symptomatic treatment.

#### CASES OF ACUTE FEBRILE ILLNESS IN WHICH FEVER IS A PREDOMINANT SYMPTOM AND SIGNS POINT ONLY INDEFINITELY TO THE ABDOMEN

**Typhoid and Paratyphoid Fever.**—Prominent among cases of this group are typhoid and paratyphoid fever. The onset is generally insidious but may be abrupt. In either event relatively high fever unexplained by any definite physical findings for some days is the rule. Fever reaches its height in from two to seven days, then fluctuates within the limits of 1 to 3 degrees for a variable period before subsiding gradually. Diagnostic signs are slow in appearing. The spleen is not palpable before the end of the first week, often later; rose spots which are far less constant in children than in adults may appear in the second week. It should be borne in mind that a mild leukocytosis is about as common as leukopenia, especially in the younger children. Constipation may be present

throughout the illness. Stool, blood and usually urine cultures are positive early, but the Widal reaction is not usually present until the tenth or even the twelfth day.

**Bacillary dysentery** is today a far more common disease among infants and children in this country than is typhoid. Fever is a prominent symptom, varying from slight elevations in mild cases to very high in severe ones. Vomiting, pain and diarrhea generally appear concomitantly with the fever but may be delayed for some hours, and the typical blood-streaked mucous stools may not appear for another day or even more. Blood is not usually present in great amount, but in the occasional case in which it does occur the differential diagnosis from intestinal obstruction is aided by the early appearance of fever in dysentery. Both conditions may show mucus free from feces, but that of intussusception contains very few cells while that of dysentery shows abundant polymorphonuclear cells.

The diagnosis of acute bacillary dysentery may be tentatively made when fever, toxemia, abdominal pain and tenderness are accompanied by diarrhea with bloody and mucous stools. Absolute diagnosis demands the recovery of the dysentery bacillus from the stool or positive agglutination tests (obtainable from the seventh to the fourteenth day after onset).

**Amebic dysentery**, rare in this country, is more gradual in onset. It is possible to demonstrate amebae in freshly passed stools kept warm. There are few cellular elements to be seen, polynuclear cells being rare among these. The blood shows a marked lymphocytic leukocytosis in contradistinction to the bacillary form where it is only slight and polynuclears are in the ascendency. In subacute and chronic cases recurrent attacks of fever and bloody mucous stools with pain and tenderness may alternate with periods of apparent recovery.

**Ulcerative colitis** shows many of the characteristics of bacillary dysentery in its later stages; but seldom produces high fever or considerable toxemia. Final differentiation must rest on stool cultures and agglutination tests.

## CASES WITH AN ABRUPT ONSET AND SYMPTOMS POINTING TO AN ACUTE SURGICAL ABDOMEN

Acute surgical conditions involving the abdomen ordinarily have pain as their primary presenting symptom and the origin of fever is not long obscure. The presence or absence of fever is however frequently of diagnostic importance especially in those children who are too young to tell of their pain.

**Acute Appendicitis.**—The progressive appearance of pain, vomiting, localizing tenderness and then leukocytosis and fever is not apt to leave one long in doubt as to the cause of the latter. It is well to bear in mind, however, that even in an advanced appendicitis the temperature may not be above 100° or 101° F.

**Chronic Appendicitis.**—Fever is even less apt to be the cause of quandary in chronic appendicitis, mechanical factors gaining importance. Bouts of fever with the recurring attacks may however occur.

**Peritonitis.**—The frequency with which appendicitis in small children leads to perforation before operation, and is followed by peritonitis is too well known to need emphasis. In such cases the cause of fever is generally only too apparent. It is rather in the cases in which peritonitis develops as a primary infection or as an extension from some abscess more obscure than that of an appendix, that fever may be of undetermined origin for a variable period.

**Primary pneumococcus or streptococcus peritonitis** is usually abrupt in onset with fever and vomiting. The temperature is generally high, 103° to 105° F. Older children will complain of pain and the abdomen is soon distended and tympanic. Rigidity may be marked but in the younger children this sign cannot be depended upon. The condition occurs most frequently in girls and is thought sometimes to have its origin in vaginal infection.

The possibility of pneumococcus or streptococcus peritonitis must be borne in mind when a patient with nephrosis develops fever of otherwise unexplained origin, accompanied or followed by vomiting, pain, leukocytosis and other though

vague localizing signs. The appearance of this condition in the course of nephrosis or of nephritis with a nephrotic syndrome is not rare or casual.

**Abscesses in the abdominal region** may long remain the cause of fever of unknown origin, then finally rupture into the peritoneum and excite peritonitis. In children the most frequent of these abscesses are associated with Pott's disease, perinephritis and cellulitis of the abdominal wall. Peritonitis occasionally follows infection of the female genital tract, even from a gonococcus vaginitis. It may result from extension of a pleural empyema through the diaphragm. The symptoms and signs are those of empyema and differentiation will usually only be made by *x*-ray.

**Subphrenic abscesses** may also have their origin in *abscesses of the liver*. These are very rare, occasionally occurring secondary to suppurative pylephlebitis from infection of the umbilical vein. Seven of 34 cases collected by Musser were due to migration of round-worms into the hepatic ducts. Fever is a prominent symptom and usually of the hectic type. It is accompanied by chills and followed by sweating, prostration, vomiting and diarrhea. Jaundice is only irregularly present. The liver is generally enlarged and tender. Aspiration of "liver pus" represents the only positive diagnosis. Duration from the beginning of symptoms is usually one to two months. Prognosis is poor, treatment is surgical unless the abscess is secondary to amebic colitis.

**Acute pancreatitis** is very rare. The main symptoms are epigastric pain, vomiting, constipation, fever. It stimulates acute intestinal obstruction and acute peritonitis. Diagnosis is generally made only after laparotomy.

#### CASES OF FEVER OF OBSCURE ORIGIN IN WHICH THE SYMPTOMS SIMULATE THOSE OF AN ACUTE ABDOMEN

A syndrome rarely discussed in texts and journals though so common in the experience of every practitioner among children, is that which, for want of a better name has been called "**intestinal grippe**." Fever, vomiting, abdominal pain

and diarrhea occurring in any possible combination and varying in type and severity in different epidemics, may so closely simulate appendicitis as to render diagnosis difficult. Many of these cases show a leukopenia which is helpful in differentiation. As indicated, fever may occur alone, in which cases explanation of its origin may be impossible except on the basis of the presence of the disease in epidemic numbers. The condition is usually of short duration and only moderate severity except in the occasional case in which the vomiting becomes persistent and attendant symptoms develop due to this fact. The causative organism has not been determined.

Fever may be the sole finding in the early stages of **acute rheumatic fever**. Before carditis or joint manifestations are demonstrable, abdominal pain so severe as to be confused with appendicitis occasionally occurs. Such cases have at times come to operation, revealing diffuse congestion of the peritoneum without evidence of pyogenic infection. The same is true of acute infections of the upper urinary tract, or non-tuberculous mesenteric adenitis and in the course of septic sore throat.

**Food Poisoning.**—How frequently the physician must fall back on the diagnosis of "food poisoning," "acute indigestion," "gastro-enteritis," "digestive upset," "ptomaine poisoning" and the like, will be known only to himself. In what percentage of cases the symptoms of diarrhea and fever, usually accompanied by nausea, vomiting and abdominal pain are unjustly attributed to bacterial food infection will depend upon the care and honesty with which the individual makes his diagnoses.

Such infections are caused by bacteria of the paratyphoid-enteritidis group which includes *Bacillus paratyphosus* alpha and beta, *B. enteritidis*, *B. suipestifer* (a secondary invader in hog cholera) and *B. aertrycke* (a name applied to *B. suipestifer* of human origin). Onset is usually sudden, occurring in from six to twelve hours after the infected food is eaten. In some instances symptoms appear so quickly after its ingestion that some investigators incline to the view

that a toxin preformed in the food by the bacteria is responsible. (The term "ptomaine poisoning" should not be used in such cases however and should be entirely eliminated from medical nomenclature.) There is the widest discrepancy in the severity of symptoms in different outbreaks and in individuals in a given outbreak. They vary all the way from general malaise and nausea without fever, to prostration and shock eventuating in death.

Fever is present in a typical case; in one of moderate severity beginning soon after the onset of gastro-intestinal disturbance and rising rapidly to  $102^{\circ}$  to  $104^{\circ}$  F.

Ordinarily in institutional and other group outbreaks diagnosis is not difficult. Children, however, are more susceptible than adults and not infrequently a child alone in a household may be affected. With the rapidity of developments in appendicitis in mind, the physician will be faced with the necessity of early decision. It is here that the fever becomes of diagnostic importance. In food poisoning the temperature is higher in proportion to the amount of pain than in appendicitis.

Occasionally, after a typical acute onset the fever may persist for weeks. This is most frequently the case when *B. paratyphosus* is the infecting organism. We have recently seen, however, several cases in which long spells of irregular fever accompanied by normal stools have finally been explained by the finding of *B. aertrycke* or *B. suipestifer* in the stools. The importance of making stool cultures is emphasized by these cases.

Outbreaks of "food poisoning" after banquets have been traced to the use of eating utensils to which silver polish had recently been applied and insufficiently removed by washing.

**Botulism** is caused by a true bacterial toxin produced by the *Bacillus botulinus* and found most frequently in home-canned vegetables, fruits, and meats. In about one third of the cases there is initial nausea, vomiting, diarrhea, abdominal pain and fever which develop a few hours after the ingestion of the food and are probably caused by local irritation of the gastro-intestinal tract by the spoiled material. These symp-

toms generally cease as soon as the typical symptoms of intoxication develop some twenty-four to forty-eight hours later. The typical case of botulism is characterized by disturbance of vision, difficulty in talking and swallowing, persistent constipation, marked muscular weakness, absence of sensory disturbance, subnormal temperature and rapid pulse.

The condition is included here largely because in 2 of 3 proved cases in children recently seen by one of us, it was impossible to demonstrate any of the above described symptoms; they had a profuse and prolonged diarrhea and fever of 100° to 101° F. for some days. In the third case, which was fatal, prostration was so great from the time of onset of symptoms to death forty-eight hours later that aside from the extreme weakness it was possible only to demonstrate dilated and relatively fixed pupils. This patient had high fever for at least twenty-four hours before death and no intercurrent infection was found at autopsy to account for it.

**Epidemic jaundice** starts with symptoms no more definite than low-grade fever, lassitude, irritability and anorexia. It may prove extremely difficult to elucidate the cause of the fever until jaundice appears, which is usually on the third or fourth day but may be delayed even as late as the twelfth day. Next to jaundice, fever, which may reach 104° F., is the most constant symptom. Abdominal pain localized in the right upper quadrant is a common complaint. The disease occurs most commonly in children and young adults in institutional epidemics which simplifies diagnosis, but sporadic cases do occur.

The causative organism has generally been considered undetermined, the condition being distinguished from *Weil's disease* by its lesser severity, absence of hemorrhages in the skin and mucous membranes, absence of hematuria and repeated failures to obtain *Leptospira icterohemorrhagiae* from individuals with the disease. In a recently reported epidemic in a religious school, however, this organism was recovered repeatedly from the holy water fonts though not from the patients. This might be considered to lend some additional credence to the view that an attenuated form of this organism is the cause of epidemic jaundice.





## FEVERS DUE TO DISEASES OF THE URINARY TRACT

MITCHELL I. RUBIN

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THE urinary tract is notorious for its ability and frequency in harboring the cause of obscure fever. Not infrequently, however, it is unjustly incriminated. Clinicians have so often been misled in the early diagnosis of pyogenic disease of the kidney that it has now become just another case of "The Boy Who Cried Wolf." The most important single sign of infection in the urinary tract is pyuria. Since this one sign is of such diagnostic importance it seems wise to discuss the significance of pus in the urine *per se*.

1. **Pyuria ("Pyelitis").**—The freshly passed urine is best examined after thorough shaking, placing a drop under a coverslip. Normally in boys the uncentrifuged urine contains 2 to 3 leukocytes per low-power field (20 to 30 per cubic millimeter), while for girls the normal number of leukocytes is from 6 to 8 (60 to 80 per cubic millimeter). In a study of the urinary cell count in a large series of febrile children after tonsillectomy, carried on at the Children's Memorial Hospital in Chicago, a sharp increase in the number of leukocytes was found. This increase of cells returned to normal when the temperature subsided. In these cases no evidence of urinary tract infection was demonstrable. Often in other febrile disturbances there is an increase in the urinary cell count which returns to normal with a subsidence of the fever. In girls the commonest cause of pyuria is vaginitis.

Not every specimen in a case of so-called "pyelitis" (pyuria) shows an increased number of pus cells; often there are none at all at the beginning of the disease. For this

reason several examinations over a period of many days are necessary. The fever usually shows an inverse relationship to the quantity of pus in the urine, the pus often appearing only when the temperature has fallen to normal. There are cases where infection of the urinary tract is only demonstrable by the presence of a colon bacillus bacilluria, for that reason urine cultures should be made before a patient with a urinary infection is discharged as cured.

The commonest instances where the urinary tract is the cause of obscure fever are cases of so-called "pyelitis." From pathological studies it seems that those instances where the pathology is limited to the pelvis of the kidney must be uncommon. At autopsy infection in the kidney substance as well is most often found. However, it is to be remembered that the mild cases do not succumb. In this disease the fever is usually high and fluctuating for two to three days, then subsides gradually or falls by crisis. The association of this type of fever with chills in children should suggest the possibility of pyelitis. In infants collapse attacks might replace the chills, as is seen in malaria. Abdominal discomfort, urinary frequency and dysuria are frequently associated. Rarely does muscle spasm and pain over the kidney region denote pyelitis. When these are present infection in the perinephric space or the kidney parenchyma itself should be suspected. Often there are symptoms involving the gastro-intestinal tract and central nervous system during the attack. Febrile attacks of pyelitis frequently recur. Between the attacks the urine may be free of pus, the only evidence of infection being bacilluria. The patient can only be considered cured when the urine is sterile.

Low-grade fever in chronic urinary infection may persist for weeks or months. When it is associated with continued pyuria, a congenital malformation of the urinary tract with secondary infection must be considered. It has been our custom to study the patient for the possibility of urinary tract malformation if pyuria persists for two months after adequate medical care. There are few symptoms save those of obstruc-

tion to the passage of urine or late signs of kidney insufficiency in cases of congenital urinary malformation when infection is not present. At times the patients go for years before infection takes place. In most cases the instillation of a sodium iodide solution into the bladder will demonstrate by means of the x-ray when the patient's buttocks are elevated, a reflux into abnormally dilated ureters and kidney pelves. The valve type of posterior urethral obstruction allows the catheter easily to enter the bladder but prevents the passage of the urine from the bladder out into the urethra.

2. **Carbuncle or multiple abscesses of the kidney** are usually associated with obvious infection elsewhere, usually in the upper respiratory tract. Often, however, when the patient first comes under observation, the respiratory infection has cleared and the cause for the fever has now become obscure. The urine in many of these cases is free of pus. When pyuria is present along with the local signs of kidney involvement such as pain and tenderness, the diagnosis is not obscure. In all cases of unexplained fever the urinary tract should be suspected. Since septicemia is so often present in these cases of severe kidney infections the temperature is typically septic. The infecting organism here is usually the hemolytic streptococcus or staphylococcus. The blood shows a marked polymorphonuclear leukocytosis.

3. **Perinephric abscess** is not a rare cause of obscure fever and like osteomyelitis is often not diagnosed simply because it is not considered among the possibilities. The majority of cases are undiagnosed until the abscess fills the flank and there are local signs of abscess. Since in about one half the cases pyuria is not present, the kidney region is not suspected as the cause for the fever. In routine examination the kidney region is too often overlooked; this probably accounts for the many instances where the diagnosis is not made. The type of fever here is that of sepsis, fluctuating widely, and chills may be present. One of the characteristic signs is flexion of the leg on the involved side due to psoas muscle spasm resulting from irritation by the abscess. The origin of peri-

nephric abscess is embolic, often the abscess results from the rupture of an abscess in the kidney cortex into the perinephric fat.

4. **Tuberculosis of the kidney** as a cause of obscure fever is rare in early life. When the kidney involvement is a part of a generalized tuberculosis, as it usually is, there often are no characteristic symptoms. When the lesion in the kidney is the major one, pain and tenderness in the kidney region with pus and blood cells in the urine help to make the diagnosis. A positive tuberculin skin reaction and x-ray studies of the chest further aid in arriving at the cause for the fever. The presence of tubercle bacilli in the urine clinch the diagnosis. Bladder symptoms are much less common in children than in adults with this disease.

5. **Cystitis** alone is unusual in children. Because of the local symptoms, dysuria, frequency, pain, and the finding of pus in the urine, cystitis is rarely a cause of obscure fever.

6. **Urinary calculi**, because of their characteristic symptoms, pain, pyuria, and hematuria, are not a common cause of obscure fever.

7. **Neoplasms** of the urinary tract save for those in the kidney are very rare in childhood. Those of the kidney are uncommon and usually produce no fever until late in the disease. When the patient is admitted to the hospital with such a tumor, the disease is usually well advanced. The first symptom that seems to attract the mother's attention is an abdominal mass. By this time the disease has progressed in most instances beyond repair. When these patients are brought to the hospital fever is usually well established and continues on until death. The temperature curve is of the septic type but the fluctuations are less pronounced. The blood may show only a slight leukocytosis. The urine contains albumin, red blood cells, and leukocytes. On physical examination aside from the cachexia the abdominal tumor is the only finding. Rarely does true metastasis occur, the tumor spreading by direct extension.

## FEVERS DISCUSSED FROM THE STANDPOINT OF CENTRAL NERVOUS SYSTEM DISEASE

T. S. WILDER

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THE symptom of fever (without signs which point to an organic cause) is often the sole warning of an infectious or other lesion of the central nervous system. Sooner or later localizing signs and symptoms will usually develop, *provided one waits for them*. If too much time is lost, however, in making a diagnosis, the chances of effective treatment are materially diminished. One may say, of course, and rightly, that this is true of all obscure febrile states. Yet disease of the brain and its coverings carries graver implications, and in dealing with it delay is perhaps just a bit more serious, than is the case with the generality of disease involving other parts of the body.

The mere presence of fever suggests infection, and in most instances infection will prove to be the responsible agent. We shall therefore consider it first, taking up later the more remote causes of hyperpyrexia wherein an invading organism is not involved.

Infections of the central nervous system, by and large, can be counted upon to furnish us with signs which direct our attention to that particular part of the body. It is unnecessary to review the wide variety of neurological effects which one may encounter, since we are not dealing, here, with the conventional manifestations of these diseases, but rather with the exceptional, atypical, phenomena.

1. **Meningococcic Meningitis.**—Among the different types of meningitis perhaps this one most frequently fails to furnish us with classical signs during the first week or two

after its onset. One reason for this may be the fact that there is considerable variation in the pathogenicity of various strains of the meningococcus.

Hence, one sees now and then a child with moderately high fever, and general symptoms of mild toxicity, who does not exhibit stiffness of the back or neck, exaggeration of the reflexes, convulsions, or any other signs of neurological disturbance. And yet, after a varying amount of delay, one discovers the patient has meningitis. The following 4 cases, from four different hospitals, may serve as illustrations.

(a) A female infant, eight months old, was brought to the hospital with the complaint of diarrhea, and a temperature of around 104° F. The respirations were quite rapid, and the admission diagnosis was tentatively that of primary pneumonia. There were no obvious signs pointing to the central nervous system. The stools proved indeed to be frequent and loose. The expected pneumonia did not materialize. This infant, however, had a "cephalic" type of cry, a high white count, and after the lapse of a few days lumbar puncture was performed on those slender indications. There was marked pleocytosis, with meningococci present, and following a short course of treatment the infant recovered completely.

(b) Another child, aged three years, was brought to the hospital with fever, moderate toxicity, and complete absence of signs pointing toward a cause. The child was observed for eight or nine days, during which time the usual laboratory procedures were carried out. Finally, purely to rule out a central nervous system infection, lumbar puncture was done, and pleocytosis with meningococci established the correct diagnosis.

In this child, likewise, a minimum of treatment effected complete cure, suggesting that the infection was due to a strain of low virulence.

(c) A girl of four years was admitted to the hospital with a temperature fluctuating between 103° and 105° F. Again physical examination was essentially negative, except for signs referable to a moderately severe generalized infection. Three or four days after admission it was noted that a macular erup-

tion was present on the trunk and abdomen. Remembering that meningococcic meningitis is often called "spotted fever," a lumbar puncture was done, and this, of course, immediately revealed the true nature of the disease.

(d) A boy of ten months was admitted to the hospital with hyperpyrexia and some evidence of cerebral irritation. On the following day a rash appeared, which involved the whole body and face, and in fact, suggested the eruption of measles, more than anything else. But of course, other signs of measles were lacking. Lumbar puncture was done immediately, and demonstrated the presence of meningococcic meningitis, secondary, as in the preceding patient, of course, to meningococcic septicemia.

In a sense it is perhaps incorrect to refer to cases like the above as examples of fever of undetermined origin. Practically, however, they illustrate the frequency with which meningococcic meningitis fails to furnish clues as to its presence. Cases such as these justify us in attaching weight to slight indications for lumbar puncture, such as a cry, possibly cerebral, or a rash suggestive of that which sometimes accompanies this particular infection.

**2. Tuberculous Meningitis.**—This highly fatal infection is notorious, perhaps, for the inconstancy of its symptoms and signs. These vary, both in different patients, and at various times in the same patient. Usually, however, neurological symptoms of one sort or another are present. Whereas neck and spine may be of normal flexibility, one patient may have developed a strabismus or nystagmus. Another may show transitory weakness of certain muscle groups. In still another there may be bulging of the fontanel, and vomiting, suggestive of increased intracranial pressure. A certain proportion of cases, however, will at first show few signs other than severe toxicity, and possibly stupor. The temperature may be very slightly elevated, that is from 100° to 101° F., or it may be much higher, and there may be such general symptoms as anorexia, loss of weight, diarrhea, dehydration, etc. Usually the infant or child exhibits marked prostration and list-



lessness, which in themselves may suggest to one the possibility of tuberculous meningitis. In such situations, of course, lumbar puncture is "de rigueur," irrespective of whether the tuberculin test is positive or negative.

**3. Meningitis Due to Streptococcus, Staphylococcus, Pneumococcus, Pfeiffer's Bacillus, Colon Bacillus, and Other Common Organisms.**—In general, it may be stated that meningitis due to these particular pathogens runs a more fulminating course than the two previously mentioned types, and that the characteristic signs and symptoms are therefore almost invariably present. Marked rigidity of the neck, marked opisthotonus, and frequently convulsions are to be expected, so that one is rarely long in doubt as to the situation. Here again, however, the patient occasionally may be met whose signs of meningitis are submerged under the toxicity of an already existing acute infection to which the meningitis is secondary. In such instances lumbar puncture is called for, if only to clarify the situation and assist in prognosis.

In this group also may be included certain rare forms of meningitis such as that caused by the lactic acid bacillus, and that caused by any one of various strains of organisms which may be classed as "molds." These infections usually develop out of a clear sky, and exhibit the same signs as the more usual types of meningitis. Whereas the prognosis may not be as hopeless as in the case of streptococcus or staphylococcus infections the difference is not great.

**4. Poliomyelitis.**—With this disease an early diagnosis is desirable from the public health viewpoint, regardless of the fact that its achievement does not materially affect the outcome. During an epidemic, when, so to speak, infantile paralysis is "in the air," preparalytic diagnoses are not hard to make.

The sporadic, isolated case, however, may present definite difficulties, one of the principal ones being failure on the part of the diagnostician to keep this disease in mind at all times. The second difficulty lies in the fact that poliomyelitis usually causes much less striking neurological signs than does menin-

gitis proper. There is usually no real rigidity of the neck but rather only a slightly increased resistance to flexion. The stiffness of the back is somewhat more marked, but this sign too may be almost wanting. Other neurological signs such as tremor, paresthesia, hyperactive reflexes, cerebral tache, and so forth, may or may not be present.

Certainly it is not uncommon for paralysis to develop in the absence of fever or discomfort of any kind. Lumbar puncture, when in doubt, will often clinch the diagnosis, but even this procedure does not always serve to distinguish poliomyelitis from luetic meningitis, encephalitis, or the so-called "lymphocytic chorio-meningo-encephalitis" (until paralysis has developed!). Such exceptions, however, do not alter the fact that careful examination and summation of the variety of signs and symptoms will usually enable one to diagnose this disease in the preparalytic stage, if one keeps it in mind.

5. **Encephalitis** deserves inclusion in the group under discussion because of the variability of symptoms at the onset, and the fact that signs of meningeal irritation may be wanting. This applies both to so-called "epidemic encephalitis," and to those supposed instances of the disease which may be the same thing but no doubt are often called encephalitis for lack of a better name. Usually there is no cervical rigidity nor a positive Kernig sign; the fever, headache, and drowsiness might accompany almost any acute infection. Hence encephalitis is a condition which at times offers obstacles to diagnosis, and should therefore be kept all the more in mind. It would appear that this disease is on the increase, also that differing strains of the virus supposed to be responsible are coming to light. This last fact accounts for the marked variations in the clinical course of the disease in different parts of the country.

The onset may be acute, or there may be a moderate fever for some time before a definite diagnosis can be achieved. Eventually, however, suggestive signs begin to show themselves, such as diplopia, ptosis of the lids, coma, convulsions, and weaknesses of the eye and other muscles. There may even

be sufficient stimulation of the respiratory rate to produce a "forced breathing" alkalosis.

A lumbar puncture will usually help in diagnosis, the spinal fluid showing a definite though slight pleocytosis in most cases. Usually the cells are entirely of the mononuclear type, and aside from a slight increase in the globulin the spinal fluid is otherwise normal.

While considering encephalitis in general, possibly mention should be made of the special situations in which it may occur following acute infections such as measles, mumps, chickenpox, pertussis, and so forth. If during the convalescence from any one of these diseases the temperature becomes elevated, the possibility of a complicating encephalitis should be kept in mind, particularly if there are the slightest concomitant signs pointing toward the central nervous system.

In this type of encephalitis, to be sure, there is more apt to be evidence of meningeal irritation, and the number of cells in the spinal fluid is usually greater than in the epidemic types. The severity seems to depend somewhat upon the preceding diseases, the mortality following varicella and pertussis being high, and that following measles and mumps being low.

**6. Acute Lymphocytic Meningitis.**—This disease entity, if such it be, has attracted considerable attention during the last two or three years. In certain respects it resembles epidemic encephalitis; in other ways suggests poliomyelitis.

Following vague prodromal symptoms of upper respiratory infection there is an acute onset of headache, malaise, fever, vomiting, and slight stiffness of the neck. The Kernig sign may be slightly positive.

Cranial nerve involvement is very much less common than, for instance, in epidemic encephalitis. Usually there is no choking of the disks, except perhaps in protracted cases.

The outstanding feature of this disease, and the one which furnishes its name is, of course, marked pleocytosis (lymphocytic) of the spinal fluid. The cell count is much higher than it is in epidemic encephalitis, or in poliomyelitis, yet the white blood count is scarcely above normal.

That this disease is due to a virus is indicated, for example, by the work of Rivers and Scott, who have reported two human cases, together with the characteristics of the infection induced in mice and guinea-pigs by intracerebral inoculation. (T. F. McNair Scott and Thomas M. Rivers, *Jour. Exp. Med.*, 63, pp. 397 and 415, March, 1936.) They have likewise shown, with the aid of Armstrong and Lillie, and of Traub, that the Rivers-Scott virus is identical immunologically with the virus independently studied by those investigators. The infection may occur in mice and guinea-pigs and monkeys, as well as in man, but appears not to be highly contagious.

6a. **Acute Aseptic Meningitis.**—This term was coined by Wallgren, in 1925. (A. Wallgren, *Acta pediat.*, 1925, 4, p. 158.) It may be applied to those types of meningitis occasionally encountered, which cause pleocytosis of the spinal fluid (mainly mononuclear) without demonstrable organisms. Naturally the term covers a wide field, including the above-mentioned acute lymphocytic meningitis. Evidence at hand indeed indicates that there are a number of different viruses which may be responsible for much the same clinical picture. For instance, Rivers and Scott have shown that the serum of many patients convalescing from "acute aseptic meningitis" does not inactivate their virus. A recent instance of this is an epidemic which occurred in Philadelphia during the fall of 1935. The syndrome was one of severe headache, photophobia, occasional convulsions, a good prognosis, and freedom from sequelae. Yet this so-called "Philadelphia headache disease" has already been shown by Rivers and Scott to differ immunologically from their "acute lymphocytic meningitis." Certainly hundreds of cases must have occurred, when one considers the fact that a series of 45 was reported by one hospital, and that all other hospitals with which we are acquainted cared for a number of patients with what appeared to be the same disease.

Practitioners, however, soon came to regard the syndrome rather lightly, owing to the fact that nearly all cases ran a rapid course without apparent sequelae. And yet in any individual patient the symptoms were severe enough at the onset

to be alarming, particularly since diagnosis was not at first apparent. Occurring in children of all ages (less frequently in adults), the onset with slight or moderate fever suggested a central nervous disturbance, yet such signs as rigidity of neck and back, positive Kernig, etc., were usually indefinite, or lacking. In some patients the reflexes were hyperactive, but in others appeared to be either diminished, or normal. Subjective symptoms were definitely more striking, although there again considerable variation was observed. Most patients, for instance, complained chiefly of headache, some of vertigo, others of pain in the eyes, and others of marked disturbance in vision, even to the point of temporary blindness. Although spinal fluid findings suggested poliomyelitis, convulsions were far more frequent than in that disease. Moreover, the minor signs and symptoms, taken as a whole, were decidedly different.

The mortality was practically nil, and no cases were followed by paralysis of any sort. It has been said that this condition represents a new disease, but others feel that we have had it with us for years, and that in the past it has been confused with abortive poliomyelitis. It is highly probable that the involuntary statistical inclusion of syndromes of this sort in the mortality records of various outbreaks of poliomyelitis explains the curiously wide fluctuations in death rate characteristic of the latter disease. Indeed, it would be difficult to prove that the two were separate clinical entities unless, as occurred in Philadelphia, numerous cases of the former were seen during a short period of time without manifesting any of the expected sequelae of infantile paralysis, and in the absence of an epidemic of the latter.

With increasing recognition of this and allied conditions, more certain differentiation between them and poliomyelitis will no doubt be possible. Progress must necessarily be slow, however, owing to the notorious difficulties inherent in the study of virus diseases.

**7. Syphilitic Meningitis.**—Occasionally meningo-vascular syphilis may be responsible for fever and other evidences of acute infection without striking neurological signs. Of

course, a history of syphilis will be helpful, and a Wassermann test on the spinal fluid will usually establish the correct diagnosis. In this connection it should be remembered, however, that a patient whose blood Wassermann is negative may have a positive spinal fluid. Indeed, Wm. C. Menninger and Leon Bromberg (Jour. Lab. and Clin. Med., vol. 20, p. 628, April, 1935) state that 31 per cent of a group of 500 cases of neurosyphilis had a negative blood Wassermann test. Hence, when one gets as far as the spinal fluid in a case of undiagnosed hyperpyrexia, and when the cytology is suggestive, a Wassermann or equivalent test should by all means be performed. There will be times when this test is absolutely necessary in differentiating between central nervous system lues and such conditions as poliomyelitis, encephalitis, and tuberculous meningitis.

8. **Brain Abscess.**—Often one of the most obscure intracranial lesions, from the standpoint of diagnosis, is that of *chronic cerebral abscess*. As everyone knows, symptoms may be almost entirely lacking. (Of acute fulminating brain abscess, such as may follow infections of the mastoid or accessory sinuses, this is of course not true.)

A chronic brain abscess may be entirely asymptomatic aside from a slight afternoon rise in temperature, headache, and perhaps some leukocytosis. (Indeed, even these signs may be absent.) At this stage, of course, no one could be blamed for failing to undertake the rather complicated procedures which might lead to a diagnosis. However, one can at least keep the possibility in mind, and can watch carefully for symptoms of pressure, and for the first localizing signs that may appear. One will then be ready to resort to lumbar puncture, ventriculogram, or to neurosurgical consultation as soon as indications arise.

9. **Pachymeningitis**, although rare, deserves mention, since it too may cause a slight elevation of temperature, and since it is one of those conditions which more often than not, perhaps, is first diagnosed at autopsy. In the later stages, of course, pachymeningitis may be suspected on the basis of

increasing malaise, fretfulness, and progressive enlargement of the head. Ophthalmic examination will then probably reveal retinal hemorrhages, and insertion of a needle into the subdural space will often disclose xanthochromic or hemorrhagic fluid. Certainly, however, the disease becomes far advanced, in many cases, before one can suspect its presence.

10. **Other infections**, involving the central nervous system could be listed ad nauseam, but they need not be mentioned here, because of rarity, or because in some instances they even lack a name. Suffice it to say that atypical manifestations of infection are always turning up, and that from time to time even a new clinical entity is described.

The fact that occasionally a patient is seen with central nervous involvement of a sort which can hardly be classified is illustrated by the following case notes:

A ten-month female infant was admitted to the hospital with an upper respiratory infection, and a high temperature. During the course of six weeks the fever gradually subsided, and the spinal fluid which showed originally 134 cells, largely mononuclear, continued for nearly six months to have an abnormally high, though diminishing number of cells. The child improved slowly, and eventually appeared to have recovered completely. Diseases such as typhoid, syphilis, meningococcic meningitis, etc., were ruled out, and cultures of the spinal fluid were at all times negative. No organisms were discovered on any occasion. The tuberculin test was mildly positive, and the diagnosis lay perhaps between tuberculoma and a low-grade brain abscess. No definite decision was made regarding the cause of the abnormal signs, and at no time were there any indications pointing to localization of a lesion in the central nervous system. Conceivably this patient may come down with tuberculous meningitis in the future, or may develop evidences of infection somewhere in the brain.

Thus far we have discussed only causes of an infectious nature for obscure hyperpyrexia originating in the central nervous system.

Infection, naturally, is most frequently proved responsible,

but, occasionally one has to consider other possibilities. These divide themselves roughly into 3 groups: *first, mechanical lesions* acting upon the heat regulatory mechanism of the central nervous system, *second, toxins or drugs* which also affect that portion of the brain, and *third, disease* which does likewise.

11. **Mechanical factors** are of such great variety that we cannot here attempt a listing of them. In brief, any trauma which injures or causes hemorrhage in the midbrain may produce hyperpyrexia, which sometimes persists for a long time after the acute effect of the lesion has subsided. To prove this point is often difficult, and to influence the natural course of the process is hardly to be hoped for.

12. **Toxic substances** or drugs may cause fever by acting partly, no doubt, on the midbrain, though usually the most obvious lesions as reported at autopsy are more generalized, and consist in widespread hemorrhagic "encephalitis" (so called) together with myelitis. This may occur, for instance, following intravenous arsphenamine. The symptoms as reported by M. A. Glaser, C. P. Imerman, and S. W. Imerman (Amer. Jour. Med. Sci., vol. 189, p. 64, January 9, 1935), consist of headache, vomiting, nervousness, dizziness, cyanosis, and hyperpyrexia. To be sure, the course is usually fulminating and the history does suggest the cause; but that an actual hemorrhagic encephalopathy can occur under these conditions is worth bearing in mind.

Other drugs known to cause similar effects include salicylates, of which methyl salicylate is perhaps the most toxic, so far as the cerebral cortex is concerned. Lead, also, under certain circumstances may cause fever as an effect of the encephalopathy for which it is responsible. The prognosis, once a diagnosis has been made, is grave, but depends in part on the severity of the intoxication, and in part on the sensitivity or susceptibility of the individual, since a fatal outcome may result from comparatively small amounts of the drug or poison. It should not be forgotten that still other drugs, with a more general effect can likewise cause fever, examples being, atropine, phenobarbital, nirvanol, etc.



13. Disease affecting the central nervous system in such a manner as to produce obscure fever groups itself according to its local effect rather than according to its nature. Thus we have a wide variation from which to pick a few examples. For instance, it sounds somewhat far fetched to say that if a child will not take his orange juice he may end up with a "stroke," and die with a temperature of  $108^{\circ}$  or  $109^{\circ}$  F., but such cases are by no means rare. As a matter of fact, when a child admitted to the hospital with scurvy develops a fever not accounted for by any other condition, one should consider carefully the possibility of intracranial hemorrhage, and too often may find at autopsy that the thing can readily occur.

Similarly any anomaly such as an aneurysm or an arterio-venous fistula, or any weakness of the vessel walls or thrombus, which may result in hemorrhage in the midbrain area, can produce hyperpyrexia.

To these also may be added blood dyscrasias such as purpuras, leukemias, hemophilia, in short anything which may, under rare circumstances, cause bleeding in the vital portion of the brain.

Finally, although brain tumor is not often the cause of fever, the exceptional case may be encountered where hyperpyrexia is an early and persistent symptom. As an extreme example Cornelia de Lange (*Acta Pediat.*, July, 1933, quoted in the 1933 Year Book of Pediatrics) reports the case of a child who exhibited a fever of six and one-half years' duration, with only occasional days of remission. The evening temperature was higher than the morning, usually reaching  $102^{\circ}$  F., by rectum. Signs and symptoms were chiefly those of progressive weakness accompanied by pain. There was profuse perspiration, and muscle atrophy developed. Autopsy revealed, among other things, a tumor in the medulla, together with a spindle-shaped enlargement of the thoracic cord. This tumor, the author believes, interfered with inhibitory impulses of the heat-regulating fibers passing through the cervical cord.

## FEVERS DUE TO MISCELLANEOUS CONDITIONS

CHARLES C. CHAPPLE

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It would appear advisable to give a short summary of the usual clinical picture of each disease which can present fever of obscure origin as one of its features. To discuss the ramifications and variations of each is neither possible nor justifiable here.

**Dehydration Fever.**—This fever is common in the newborn before the mother's milk has become sufficient and while the child is on a low fluid intake. At this time the condition is a true clinical entity. Later in infancy dehydration must be considered at all times as an added factor in the etiology of temperature elevations. These babies have skin which lacks elasticity and feels dry to the touch. The most rational means of diagnosis is likewise the most rational method of treatment. Supplying fluid by mouth, subcutaneously or through any of the other routes brings an immediate drop in the fever and a loss of the skin signs. Should the question of diagnosis appear more complex it is possible to be absolutely definite by laboratory procedures. The blood urea and chlorides are routinely increased and the serum calcium, as well as the volume percentage of oxygen capacity, is above normal limits.

**Sepsis of the Newborn.**—Fever is expected in this disease though occasionally it fails to appear. Protracted and severe jaundice is the common finding of significance. Loss of weight, pallor, and increased sweating closely follow the jaundice in frequency of occurrence. Other signs are more variable in their appearance. Nausea and vomiting or diar-

rhea may be present. Petechiae seldom fail to be visible but their arrival may be delayed.

One should look first for a possible etiological source. An infected umbilicus or an apparently mild impetigo may be the focus. Rarely, none can be located. A blood culture should be done at once to establish the diagnosis. The white blood cell count gives evidence of severe infection.

**Mechanical Prevention of Evaporation.**—Prematures are notoriously thermolabile. To a somewhat less degree children with fevers are also thermolabile. In these two groups especially, blankets, heating cradles, and even casts may become important producers of hyperpyrexia. Post-anesthesia technic requires that the child be kept warm. If the same routine be followed by nurses the year round the incidence of high fever will be much greater during the summer months. Common sense can keep the number of blankets seasonal and reasonable.

**Teething.**—In the thermolabile infant teething can be the cause of high fever. The tendency is to attribute far more symptoms and signs to the teeth than they cause. However, when all other possibilities are eliminated the gums must be considered. Commonly they are swollen and reddened when they are the source of discomfort and fever. Occasionally they appear to be innocuous but the constant chewing and biting of the infant puts them under suspicion.

**Abscessed Teeth.**—An obvious defect in the enamel may not be apparent although an abscess be concealed at the root of the tooth. Careful examination along the gum may reveal the discharging point of a "gum boil." Local lymphatic swelling and tenderness can be discovered.  $\alpha$ -Ray examination makes the diagnosis clear.

**Roseola Infantum—Exanthem Subitum.**—This is a disease occurring only in infants and children under three years of age. The fever is high, 103° to 105° F., for several days before any physical signs beyond a mildly reddened throat may be discovered. At the end of this period the temperature falls by crisis, a nondescript rash of the German

measles type makes its appearance, and the child is well. Unlike German measles this disease has no postauricular nor post-cervical glandular enlargement.

**Scurvy.**—Irritability, not fever, is the real characteristic of scurvy. Fever is very likely to occur, however, and may be of extreme degree when a hemorrhage reaches the thalamic region. All the signs and symptoms of this disease are due to the same cause, namely, the extravasation of blood and the distentions caused by it. This hemorrhage is most easily visible on the gums about the teeth. Where none are present, this sign is of little value. Along the bones the hemorrhage is subperiosteal, causing great pain and swelling. On the long bones it begins at the epiphyseal ends of the shaft. Because of the proximity to the joint the swelling seems to involve the articulation itself. Subperiosteal hemorrhage may be of great severity even to the production of dislocation fractures. Over the flat bones the same type of hemorrhage occurs and may progress to the production of exophthalmus.

The use of the tourniquet to produce capillary hemorrhage as a diagnostic means is not reliable. In some cases of scurvy petechiae are readily produced, in others it is impossible to produce them.  $\alpha$ -Ray evidence of the disease appears early.

Aspiration of sterile blood distinguishes the condition from osteomyelitis. This aspiration is seldom necessary as  $\alpha$ -ray evidence is obtainable at this stage. A therapeutic test of giving vitamin C should be performed simultaneously with other methods for establishing the diagnosis.

**Osteomyelitis.**—A history of an injury followed by a fever and a deep bone pain make this an evident diagnosis. In infants it can be much more obscure. Fever of increasing height is inevitably present. Prostration soon ensues. Pain, as evidenced by the irritability and moaning cry, is early and constant. One finds swelling over the involved area with sharply demarcated tenderness of extreme degree. The regional lymph nodes are enlarged and tender. The differential diagnosis usually resolves itself into a differentiation of this condition from rheumatic fever. This may not be easy.

Osteomyelitis is a much more severe infection in its local manifestations than rheumatic fever. It does not affect more than one area. The systemic signs, such as prostration, chills, and convulsions, are more usual and severe in the early stage. The white blood count and polymorphonuclear proportion is much higher than in rheumatic fever. There may be apparent joint involvement in osteomyelitis but the point of greatest tenderness is over an epiphysis adjacent to the joint itself.

Unfortunately neither condition has roentgenogram evidence in the early stages. After ten days there is a characteristic x-ray picture of osteomyelitis.

**Rheumatic Fever.**—The course of this disease is one of the most variable of the complaints of childhood. Its only stable feature is the rarity of its onset prior to the fourth year of life. Its course may range from indeterminate muscle and joint aches and pains to those scarcely distinguishable from osteomyelitis. The fever may be so slight as to be overlooked by the mother or so severe that it is septic in type. In the milder forms there may be nothing to be found until the heart begins to show involvement. Fortunately the usual case furnishes physical evidence of disease. Fever following a streptococcic sore throat or other infection makes one suspect the milder forms. Frequent nosebleed and loss of appetite are premonitory signs. Physical examination occasionally reveals subcutaneous nodules over the malleoli, the extensor tendons of fingers and toes, the scalp, and around the knees and elbows. There may be joint stiffness and abdominal pain. A postnasal drip is often present as rheumatic fever is frequently associated with pharyngitis and tonsillitis. Erythema nodosa and erythema multiforme, especially the former, are so often found in this disease that many examples of those syndromes are assumed to have a rheumatic origin. The joint involvement is one of painful motion, swelling and tenderness. It commonly attacks several joints simultaneously or successively. In this it is quite different from osteomyelitis. The laboratory reports an increased white blood cell count with a shift of the Schilling index to the left and a rapid sedimentation rate. None of

these are specific for rheumatic fever but are constant findings with it. The degree of leukocytic response may be great but not so great as a pyogenic infection would summon.

**Undulant Fever—*Brucella Melitensis*—Malta Fever.**

—Fever is one of the few constant signs found in this disease. It is associated with chills, loss of weight, increased sweating and loss of appetite. There may be constipation, abdominal pain and backache. Headache and cough with excessive nervousness and weakness are other symptoms found in this condition. Joint pain and deep bone pain are not uncommon. On examination one finds pronounced pallor, enlarged cervical nodes and commonly moderate enlargement of the spleen. The skin may have indeterminate macules and papules.

The laboratory is able to give definite evidence toward this diagnosis. The blood, urine, and duodenal contents will supply the organism when cultured in carbon dioxide. The agglutination phenomenon appears after the seventh day of the disease. The white blood count reveals a leukopenia. A cutaneous test for this disease is performed with a heat-killed broth culture of brucella diluted 1:100. Redness in forty-eight to seventy-two hours indicates past or present infection.

**Tularemia.**—The onset of this disease is initiated by fever, chills and general malaise which may increase to prostration. When the history is taken it is found that the child has been in close contact with a rodent, usually a rabbit. There is a generalized lymph gland enlargement. The cervical nodes are frequently conspicuously swollen and sometimes the disease attacks the eye, giving a severe ophthalmitis. Fever is constant in type, pursuing a characteristic course. Its duration is from one to three weeks. It has an initial rise of two or three days followed by a remission for about the same length of time and a second rise and slow fall to normal. A maculopapular rash may appear during the course of the disease. Diagnosis can be established clinically through the use of a skin test which consists of a vaccine of *Bacterium tularense* diluted 1:10,000. An area of redness appears at the site of

injection in thirty minutes to forty-eight hours if there be infection.

**Rocky Mountain Spotted Fever.**—This tick bite fever is known to occur far more widely than in the Rocky Mountain region to which it was thought restricted. Recently many cases have been reported along the Atlantic seaboard. It should be anticipated in all parts of the United States. The disease is transmitted by ticks, the *Dermacentroxenus rickettsii* being the organism involved. This disease is similar to typhus in all but two particulars. It has a shorter incubation, two to five days, and its rash begins at the wrists extending centripetally to involve the body. In all other respects the diseases are identical. See Typhus.

**Typhus Fever—Brill's Disease.**—This disease, like Rocky Mountain spotted fever, is caused by a rickettsia. In the case of typhus it is *Rickettsia prowazeki*. This organism is carried by lice and bedbugs. Its incubation period is twelve or more days. Typhus and Rocky Mountain spotted fever are identical in their course. Both have sudden severe onsets with fever, chills, and prostration. The temperature rises and stays elevated continuously. About the fourth day the rash makes its appearance. In typhus the rash begins in the axillae and extends centrifugally to involve the extremities and in so doing may be distinguished from Rocky Mountain spotted fever which spreads centripetally. Both have headache, nausea, vomiting and frequently backache and joint pains are present. Coma and delirium commonly ensue. The rashes in both are maculopapular and petechial. In both the skin signs may be accentuated by the tourniquet test. In both there is leukocytosis. The Weil-Felix agglutination reaction makes its appearance about six weeks to two months after convalescence. This is the agglutination of cultures of X19 or X2 in dilutions of 1:80 or greater, by the serum of the patients. Guinea-pig inoculation of the patient's sputum may show results before this time. The urine gives positive diazo reactions.

**Rat-bite Fever.**—As its name suggests this disease is

transmitted through the bites of rats. The organism present is the *Borrelia muris* (*Spirochaeta morsus muris* or *Spirillum minus*). The disease has an incubation period of two weeks after which there is a sudden onset of fever accompanied by chills and prostration. Muscle and neuralgic pains are marked. A bluish-red maculopapular rash appears after the height of the disease is reached. Spirochetes can be demonstrated by the dark-field method in the blood or the wound. The urine not uncommonly contains them as well. Guinea-pig inoculation will reproduce the disease.

**Relapsing Fever.**—This condition also is caused by infection with one of the various species of *Borrelia*. It is characterized by periods of fever alternating with normal temperatures each lasting five to seven days. It probably is transmitted by lice or bedbugs. There is a prolonged, recurrent fever which brings chills, muscle and joint pains, headache, vomiting and nausea with it. The spleen and liver are enlarged. On the skin are multiple petechiae. The laboratory findings are the same as for rat-bite fever.

**Malaria.**—Malaria in the child can present quite a different picture from that in the adult. The younger the child, the greater may be the variation. There is no maternal immunity transferred in this disease. Congenital cases have been described. Children acquire all three types of the disease but in the child they can seldom be distinguished by their clinical courses. Regular recurrences of the febrile attacks may be entirely absent. Chills, so common in the adult, may take the form of muscle pains in the child. The duration of the fever on each rise is shorter in childhood and the fever is more likely to occur at night than in the morning as in the adult.

The children with malaria complain of listlessness, weakness and anorexia. An attack of fever is ushered in by cold extremities, cyanosis and vomiting. One third of them have convulsions. Anemia of a hemolytic type appears and becomes progressively worse. Leukopenia may or may not be present. Hemic murmurs, enlarged hearts, and gallop rhythm occur in the more chronic cases. The spleen becomes en-



larged in the chronic ones while in the more acute the liver is more regularly swollen. In infants the liver is more frequently enlarged than the spleen.

**Malaria Inoculata.**—More and more cases of malaria are occurring following blood transfusion. The incubation period depends upon the number of parasites transferred, as in other malaria, and may be as short as three days. Commonly, it is two weeks. The course is that of malaria acquired in the usual manner. See Malaria.

**Hodgkin's Disease.**—This disease is characterized by a glandular enlargement of disputed etiology. The glands involved commonly are the left cervicals. These may be left unscathed and only the mediastinal or retroperitoneal glands touched by the disease. In any case there is a low-grade, variable fever of a recurrent order. Accompanying the fever is a loss of weight and appetite. In the further advanced cases vomiting and nausea, abdominal pain, cough, dyspnea, and epistaxis and bleeding gums may be present. Marked itching is frequently a source of discomfort to the patient. Pallor, jaundice or cyanosis may be found on inspection. The liver and spleen are enlarged and ascites occasionally occurs. The diagnosis can be established by biopsy and Gordon's rabbit inoculation test. The blood picture shows an increase in the number of platelets and monocytes. Eosinophils usually are only slightly, but may be enormously, increased. There is a uniformly widened mediastinal shadow on the  $x$ -ray plate.

**Pel-Ebstein Hodgkin's Disease.**—In this form of the disease there is a complete remission of fever at regular intervals. See Hodgkin's.

**Leukemia.**—In both the lymphatic and the myelocytic types of leukemia there is a prolonged or recurring fever usually of low degree. In both types chills accompany the rise in temperature. The symptoms are those of capillary hemorrhage. They may include cough, dyspnea, epistaxis, deafness, sore mouth, dysphagia, bleeding gums and anorexia, abdominal pains, nausea, vomiting and diarrhea. Should the hemorrhage strike the nervous system paralyzes of any order may

be encountered as well as sensory alterations. Pallor, jaundice, petechiae, retinal abnormalities, blood per rectum, may be expected on examination. The stool and urine may have positive benzidine tests or even gross blood. In the lymphatic type of leukemia cervical nodes, salivary glands, axillary glands and generalized enlargement is to be expected. In the myelocytic leukemia one finds liver enlargement primarily. Blood studies expose the nature of the malady.

**Acute Infectious Mononucleosis—Glandular Fever.**—

After an incubation period of four days to two weeks the onset suddenly occurs. Fever of 102° F., or more, headache, stiff neck and general malaise are regularly present. After four days glandular enlargement begins to be evident. The cervical nodes are especially affected. These are distinctly tender to the touch. There may be pain in the abdomen. The spleen enlarges in most instances and also the liver in the more severe involvements. There is no rash. In the early phase a leukocytosis with a high polymorphonuclear percentage may be found. This picture changes shortly to a preponderance of lymphocytes with many immature cells visible. Although the lymphocytes are increased both relatively and absolutely they are never of the high percentages found in the leukemias. Heterophil antibodies can be demonstrated.

**Sickle Cell Anemia; Sicklemia.**—This form of anemia is prevalent only among the colored race. It has been reported rarely among the Mediterranean peoples but seems not to attack the Anglo-Saxon. In Negroes sickling can be demonstrated in a high percentage but few develop the subsequent anemia. The disease is named from the form the red blood cells assume on standing in a moist preparation. The onset may occur at any age and may be either mild or severe. Commonly, a febrile attack marks the beginning of this progressive, hemolytic anemia. Weakness, lassitude, anorexia and a very low-grade fever may obscure the true diagnosis. Yellow-green sclerae, generalized itching, muscle and joint pains are frequently observed. Dyspnea, abdominal pain accompanied by vomiting, palpitation, numbness and tingling or paralysis, may

occur in the progress of this disease. One finds heart murmurs, enlargement of the spleen and occasional enlargement of the liver, on examination. Clubbed fingers are not uncommon. Delayed physical and sexual development occur in the more severe cases of this condition. Besides the sickling the blood shows evidence of hemolysis. There is a reduced fragility of the red blood cells. The hemoglobin falls to a low level and nucleated and reticulated forms of red blood cells appear. The urobilin is greatly increased in both stools and urine. An indirect van den Bergh reaction can be detected in the blood.

**Psittacosis—Parrot Fever.**—This disease may be contracted from any of the parrot family including macaws and parakeets. There is a sudden onset with a high fever. Nose pain and discharge is one of the usual early complaints of the victims. Cough and dyspnea, or nausea and vomiting and diarrhea soon appear. A macular rash occurs at the height of the disease. Diagnosis can be established by intraperitoneal injection of the sputum from infected patients into mice. Characteristic psittacosis bodies appear in the spleen of the mice so inoculated. Since the same result can be produced from either filtered or unfiltered sputum Rivers and Berry conclude that the causative organism is a virus.

**Paroxysmal Hemoglobinuria.**—Recurrent febrile paroxysms associated with hemoglobin in the urine give this disease its name. The attacks follow exposure to cold or the immersion of the hand or feet in cold water. Each attack is accompanied by chills, and nausea and vomiting. Generalized urticaria may be present. Pains in the back, the abdomen and the extremities frequently occur. The spleen is moderately enlarged.

The disease is likely to be a result of congenital syphilis. The Wassermann reaction should always be determined. An autohemolysin can be demonstrated by mixing the patient's red blood cells with his own serum at 0° C. for seven minutes. After this length of time the blood should be incubated at 37° C. for one hour (Donath-Landsteiner reaction). An attack

can be precipitated by immersion of the feet in ice water for one-half hour.

**Purpura.**—It is inaccurate to classify purpura as a clinical entity. It is a sign of disease but since it can, and does, occur as the major physical finding in some conditions it may be discussed here. It receives its various names from its predominating symptom or from its cause. Thus there is purpura rheumatica or Schoenlein's purpura, and purpura abdominalis or Henoch's purpura, as well as cachectic purpura, urticarial purpura and thrombocytopenic purpura. This last is the one of importance to this discussion. The attacks usually are initiated by a febrile period. This is of moderate elevation in the usual case. It may be slight indeed so that the purpuric areas are noted first and the temperature determined merely as a routine procedure. In these children pallor, headache, loss of appetite may be the reason for consultation with a physician. More frequently the onset is more violent. The symptoms and signs may be of any or all the systems depending upon the site of the hemorrhages. Thus there may be retinal abnormalities, deafness, epistaxis, bleeding gums and vomiting, hematuria, and hematemesis, bloody diarrhea and abdominal pain. There may be paralysis and disturbances of sensation. It may resemble meningitis. In the rheumatic purpura joints are swollen and painful. Of course, in the abdominal type symptoms relating to the gastro-intestinal tract predominate.

The diagnosis can be verified by laboratory means. The platelets which normally number 250,000 to 300,000 may be as low as 50,000 or less. The clotting time is within normal limits but the bleeding time is definitely prolonged. The tourniquet test, while not specific, may be of value as a clinical adjunct. Purpuras of the cachectic, and urticarial types, and those due to poisons, blood dyscrasias or scurvy do not have a reduction in the number of platelets.

**Subacute Bacterial Endocarditis.**—This disease does not exist in an undamaged heart. The damage may be slight, however, and difficult to demonstrate. History of a previous

rheumatic fever may be of great value in establishing the diagnosis. In subacute bacterial endocarditis there is a protracted fever with an accompanying pallor and debility. Physical signs other than those found in the heart itself may be greatly delayed in appearance. Enlargement of the spleen occurs at times. Electrocardiographic tracings will assist in the demonstration of heart damage. Orthodiagrams by the roentgenologist may be of value, but close clinical observation will eventually discover it. When it is known that there is heart damage this diagnosis becomes less obscure as a cause of fever. Characteristically subacute bacterial endocarditis progresses to give multiple minute emboli. These are most easily visible in the conjunctivae but cause more marked symptoms when they strike the capillary bed of a finger. Blood culture, however, will often demonstrate the presence of subacute bacterial endocarditis before any of these findings are evident.

## SYMPOSIUM ON COMMON OBSTETRIC AND GYNE- COLOGIC PROBLEMS OF THE FAMILY PHYSICIAN

The following clinics are included in this Symposium:

P. Brooke Bland and Arthur First: STERILITY.

Norris W. Vaux: DIAGNOSTIC MISTAKES IN GYNECOLOGY.

Franklin L. Payne: THE CAUSES OF ABNORMAL VAGINAL BLEEDING DURING  
THE PRE- AND POSTMENOPAUSAL AGES.

Margaret Castex Sturgis: TREATMENT OF HABITUAL ABORTION.

Aaron Capper: THE DIAGNOSIS AND TREATMENT OF CYANOSIS OF THE NEWBORN.

Thomas J. Costello: TREATMENT OF CHRONIC ENDOCERVICITIS AND VULVO-  
VAGINITIS.



## CLINIC OF DRS. P. BROOKE BLAND AND ARTHUR FIRST

DEPARTMENT OF OBSTETRICS, JEFFERSON MEDICAL COLLEGE

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### STERILITY

A PROPER study of a barren marriage requires equal attention to the male and female. So conspicuous is the incidence of male responsibility in our clinic that in more than 50 per cent of the patients the two mates are receiving treatment simultaneously. Every effort should be made to raise the fertility index of the male as high as possible, thus indirectly increasing the fertility of the wife with a low index.

**Male Responsibility.**—Sterility in the male may be due either to congenital or acquired conditions of the testicle, vas deferens, epididymis, prostate gland or penis, which interfere with proper development of the spermatozoa, or with the conveyance of living sperms to the genital organs.

A lowered fertility in the male may also result from either functional or organic nervous disease, especially those associated with impotence. Organic lesions may cause azoospermia, a total absence of spermatozoa; oligospermia, a marked diminution of spermatozoa; or necrospermia, the presence of feeble or dead spermatozoa.

Most of these conditions result from gonorrheal infection. Gonorrhea is a preponderating cause in both primary and secondary sterility. The toll that gonorrhea exerts in unborn lives is utterly impossible to determine or even guess, but it is believed that from 30 to 50 per cent of sterile marriages result from this disease.

Endocrine hypofunction, depressed constitutional states, exhaustion from sexual excess or obstruction in the passages



may be responsible factors. It is necessary, therefore, to obtain a genito-urinary history and make a thorough examination of the husband.

Accurate observation of the morphology, vigor and persistence of sperm motility as obtained from a condom specimen and a postcoital examination of the cervical canal are important in properly appraising male fertility.

Azoospermia is relatively infrequent, being encountered in only 5 per cent of sterile marriages whereas oligospermia is noted in over 50 per cent. The mere finding of live sperms does not absolve the male, as the chances for impregnation are in direct ratio to the number and vitality of the spermatozoa.

**Normal Male Fertility.**—A normal specimen (preferably obtained from a glass jar, warmed to body temperature and examined not later than one hour after intercourse) should reveal the following:

(1) 50 to 100 live sperms per high-power field.

(2) A one- to two-hour resistance to room temperature, the spermatozoa remaining motile on a slide under the microscope.

(3) A large number of dead sperms.

Lowered fertility is indicated when one observes a large number of amyloid bodies or more than 5 pus cells per high-power field.

Moench claims that a morphologic and biometric examination of the semen offers a method for ascertaining male fertility. A normal fertile man ejaculates less than 15 per cent abnormal sperm heads. If the head abnormalities rise to between 20 and 25 per cent, impaired fertility is to be assumed and above 25 per cent, sterility. The number of these abnormal sperm heads indicates the degree of spermatogenic disturbance and that the other sperm heads, although they may appear normal under the microscope, may not be normal.

Macomber made counts of spermatozoa and found variations between 300 million and 100,000 organisms per cubic centimeter. A count below 60 million per cubic centimeter indicates low fertility in which the sex cells seem to suffer.

According to Kurzrok and Miller, semen exerts a highly specific lytic action on the mucin of the cervix. Tests made with mucus from patients with leukorrheal discharge indicate that the digesting action of normal semen is markedly diminished by the presence of inspissated mucus. If a drop of seminal fluid is placed alongside a drop of cervical mucus under a coverglass, a number of sperms should normally pass through the cervical drop within one hour. The lytic substance of the semen may be essential in the passage of spermatozoa up the genital tract and its absence may be an etiologic factor in some cases of sterility for which no other explanation can be offered.

**Postcoital Examination.**—Cervical insemination and favorable cervical secretion are essential for the proper transmission of spermatozoa. Huhner's test which includes investigation of semen activity in the vagina and all levels of the cervical canal to the internal os, is of inestimable value. Spermatozoa seldom survive more than two hours in the vaginal pool (receptaculum seminis), but may retain vigorous motility in the normal cervix for from sixteen to twenty-four hours. The finding of nonmotile spermatozoa in the cervical canal may be due to necropermia or to hostility of the cervical secretion. It is essential to examine a condom specimen to differentiate the two conditions. A postcoital examination should be made four to six hours after intercourse. Normally 5 to 10 sperms per high-power field are obtained from the aspirated cervical canal secretion. If less are found, it is assumed that coitus is faulty or that the cervix has not been properly inseminated.

**Sterility of the Female.**—*Investigation.*—A complete and comprehensive study of the female factors in the production of sterility, includes:

1. A careful general and gynecological history.
2. A complete physical examination with special emphasis upon endocrine and pelvic study.
3. Complete laboratory studies including a serological blood test, a routine blood count, a urine examination, a basal metabolic rate determination, an estimation of the blood chol-

esterol, a premenstrual determination of the estrin hormone in the blood, an estimation of the pituitary blood hormone, a determination of the urinary excretion of estrin and anterior pituitary hormone, a study of the specific dynamic action of protein, a glucose tolerance test, eyeground and visual field examinations and a roentgenogram of the sella turcica.

4. A special gynecological examination including a study of the endocervical secretions, a postcoital examination, a tubal insufflation and, if necessary, a subsequent lipiodol injection and a premenstrual curettage to determine the presence or absence of a normal premenstrual nidatory endometrium.

*Etiology.*—The factors responsible for sterility in the female may be divided into general causes, local causes, and functional disorders. Usually there are several abnormalities coexisting.

**General Causes.**—1. *Infections.*—The acute infections, influenza, typhoid fever, mumps, scarlatina, tonsillitis, acute rheumatic fever, and acute puerperal fever may cause secondary ovarian infections and result in atrophy and sterility. Focal infection may likewise be responsible.

2. *Chronic systemic diseases* such as diabetes, renal and pulmonary disease, or profound anemia are not uncommonly associated with sterility. Chronic alcoholism, morphinism and cocaineism are also associated with sterility while in organic and functional nervous conditions, impregnation is not likely.

3. *Consanguinity.*—Sterility is not uncommon in the union of blood relations, although it is not an absolute barrier.

4. *Selective sterility* (incompatibility) refers to those individuals who do not bear offspring, although both may be fertile when united to other partners. This type is not infrequent. The cause is not known. It perhaps resides in both partners who are of low fertility, although either partner may produce offspring in a highly fertile mate.

5. *Physiological Causes.*—Women are sterile during certain physiological states, as in pregnancy, except in those rare cases of superfetation in the normal or in the double uterus. Frequently women are sterile at certain periods (safe period)

and for this reason the sexual relation is indulged in by these individuals only at this time. Physiologic sterility is, however, debatable. Knaus contends that women who menstruate every twenty-six to twenty-eight days can only conceive from the ninth to the fifteenth day of the cycle whereas those who bleed every twenty-eight to thirty days are capable of fertilization only between the eleventh and seventeenth days of the cycle.

**Local Causes.**—1. *Congenital Underdevelopment of the Genital Organs.*—This is one of the most common local causes of sterility either in the form of a rudimentary vagina or uterus, stenosis of the vagina or cervix, or an imperforate hymen.

2. *Faulty Cervical Insemination.*—It is essential that the semen reach the cervical canal directly. Severe lacerations of the vagina with prolapse of its walls, and of the cervix, allowing escape of the seminal fluid, are provocative of sterility. Dyspareunia, resulting either from psychic conditions or lesions of the vulva and vagina, may be responsible. Urethral caruncles which are extremely sensitive may set up a vaginismus. Kraurosis vulvae may not permit sexual access to be completed.

3. *Hostility of the Endocervical Secretion.*—Hostility of the cervical secretion is indicated when one finds only dead spermatozoa in this material six hours after coitus, especially if normal sperms at the same time are found in the condom specimen. Acid cervical secretions inimical to the sperms are usually found in women without infection. This biochemical incompatibility is more often associated with poor cervical drainage or ovarian deficiency with hypoplastic generative organs and precludes fertility. The hydrogen ion concentration of cervical secretion varies between 8 and 9 (*i. e.*, definitely alkaline). An excessively high acidity may occasionally cause sterility, although this is infrequent, as normal vaginal acidity is due to lactic acid which practically never exceeds 0.5 per cent. In this spermatozoa may live for hours. The hostility of excessive acid vaginal secretion has been confirmed

by conception occurring after neutralization or alkalization of the vaginal secretion.

4. *Displacement of the uterus* is not a cause of sterility if proper insemination of the cervix takes place as noted after a postcoital examination. It may, however, be indirectly responsible from the complicating inflammatory lesions of the lining membrane or the wall or by interfering with the circulation of the ovaries. Uterine abnormalities are often accompanied by other conditions which render conception impossible. Thus an infantile uterus may be associated with sterility because of infantile ovaries failing to ovulate. Acute antelexion with cervical stenosis is seldom responsible for sterility. The easy introduction of a sound with the thickness of from 2 to 4 mm. into the cervical canal is proof that no obstruction to the ascent of spermatozoa is present.

5. *Tumors*.—Neoplasms of all types, especially those involving the endocervix or the endometrium, as polyps, for example, may, if developing early, result in absolute sterility; if later, relative sterility. Fibroid tumors are the most common forms of neoplasms associated with sterility. Submucous myomas by obstructing the uterine ostia of the tubes may prevent conception or by encroaching upon the uterine cavity may cause abortion. Conception, however, may occur in fibroid of the interstitial and subserous type, especially if these are not complicated by endometrial, tubal or ovarian disease.

6. *Stenosis of the Tubes*.—Partial tubal obstruction is a common cause of extra-uterine pregnancy. Complete tubal occlusion is the most frequent cause of sterility. This may be the result of spasm, a developmental defect or an antecedent inflammation. Acquired tubal stenosis is usually gonorrheal in origin, though it may follow abortion, appendicitis, peritonitis or intra-uterine infections. Retroversion is cited as a common cause of tubal kinkage.

7. *Ovarian Sterility*.—This may be congenital or acquired. In the congenital type there is a retarded development of the ovaries closely associated with other endocrinopathic irregularities. In the acquired type inflammation of the ovaries re-

sulting in hyperplasia or sclerosis is not an uncommon cause of sterility. The antecedent pelvic infection, usually gonorrheal in origin, results in a thickened tunica albuginea which impedes maturation and rupture of the graafian follicle. Failing to rupture, the follicles become the seat of cystic degeneration. In these patients, there is often an associated endometrial hyperplasia producing prolonged menstrual flow. If ovulation does occur, an existing infarcted and hemorrhagic endometrium often prevents conception. Ovarian abscess due to gonorrhea or tuberculosis may cause complete destruction of the sexual glands. Ovarian cysts by destroying the ovarian structure or by compressing the tubes may likewise cause sterility.

8. *Contraceptives and Sterility*.—Various contraceptive measures resorted to in the first two years of marriage may produce hostile secretions and chronic pelvic congestion inimical to conception. The use of intra-uterine stems may well be considered as a cause, because of irritation, erosion and infection of the uterus and tubes. The use of strong vaginal antiseptics, as undiluted bichloride of mercury, may also be mentioned as causative.

**Functional Sterility**.—The interpretation of sterility in patients in whom a complete physical examination reveals no anatomic abnormalities in either husband or wife is a complex problem, requiring for satisfactory solution among many things an understanding especially of the interrelationship of the glands of internal secretion.

In dealing with sterility of assumedly endocrine origin, it is of paramount importance to determine, if possible, which gland is primarily responsible. From the angle of investigation, functional sterility may be conveniently divided into clinical and laboratory aspects.

Etiologically, cases of functional sterility may be due chiefly to primary pituitary, ovarian or thyroid dysfunction.

**A. Primary Pituitary Deficiency**.—Primary deficiency of the anterior pituitary lobe is by far the most common form of endocrine disturbance encountered in sterile patients. Generally speaking, this condition, if not sufficiently severe to

suppress totally ovarian function, is usually one of a mild Fröhlich's syndrome (adiposogenital dystrophy). Clinically, these patients are rather short in stature and show distinct stigmas of underactivity of the hypophysis, manifested, first, by a characteristic mammary-mons girdle obesity due to associated involvement of the hypothalamus; secondly, by hypertrichosis with masculine distribution of pubic hair, and thirdly by genital hypoplasia with menstrual derangements.

**B. Primary Ovarian Failure (Primary Hypogonadism).**—Primary ovarian failure is due to inherent deficiency of the internal secretory portion of the ovary independent of the secondary effects of the diminution of function of other glands, notably the pituitary and thyroid. Clinically, these patients present a marked contrast to those of the hypopituitary type. They represent the superlatively feminine type. They are emotional to excess, underweight, visceroptotic and intolerant to food, and experience gastro-intestinal spasticity and irritability of the nervous system.

Hypoplasia of the genital organs and irregular menstruation or amenorrhea are constant observations. Hormone studies reveal a uniformly low estrogenic level in the blood premenstrually. The most significant finding, however, is a demonstrable quantity of anterior pituitary gonadotropic hormone in the blood and urine in about 50 per cent of the patients.

**C. Thyroid Derangement.**—Thyroid dysfunction either in the form of hypoactivity or hyperactivity not infrequently is a cause of sterility.

The diagnosis is relatively easy, provided one resorts as a routine to basal metabolic studies in the investigation of functional sterility.

**Hormone Studies.**—The determination of ovarian (estrogenic) and pituitary (gonadotropic) hormones in the urine is an extremely valuable laboratory adjuvant in the diagnosis and treatment of the underlying condition as well as of allied menstrual disorders.

**Study of the Endometrium.**—The endometrium obtained

after a diagnostic premenstrual curettage yields valuable information regarding the presence of a suitable nidatory site for the implantation of a fertilized ovum. The absence of a normal secretory premenstrual phase is indicative of failure of ovulation or of a deficient corpus luteum and explains many problem cases of sterility in the regularly menstruating woman.

**Treatment of Sterility.**—A thorough knowledge of the etiological factors involved must be obtained before any course of treatment is outlined. For this reason the cooperation of gynecologist, urologist and internist in a well-organized sterility clinic is essential for a proper study of the problem.

**Diet.**—A diet low in calcium has considerable effect in reducing fertility and may even favor miscarriage. A high protein and vitamin E diet, low in calories, with the administration of calcium lactate and enough exercise to assure assimilation, is recommended. Diet is also of great value in the treatment of associated anemia or obesity. While obesity may not be the cause of sterility, it is frequently associated with evidences of diminished ovarian function which is improved by weight reduction.

**Vitamin E in Relation to Sterility.**—In the male a diet rich in vitamin E is more important than in the female. In the woman, abortion, it is believed, can be prevented by a diet rich in vitamin E. The substance is found widespread in the organs of certain plants, especially in green leaves and seeds. It is abundant in wheat germ, peas, alfalfa, lettuce, spinach and other leaves. In wheat, it is stored exclusively in the germ. In fact wheat germ oil constitutes one of the highest known sources of the vitamin. It is present in small quantities in animal tissues and in milk. It is absent in the tissues of animals which have been deprived of this vitamin by some special type of artificial feeding.

It has been suggested that vitamin E should be termed "anti-abortion vitamin," rather than antisterility vitamin.

**Tubal Insufflation.**—The Rubin test as a therapeutic measure has recently been brought to the fore. Pregnancy may follow insufflation by separating mild agglutinations and



straightening tortuous tubes. This is demonstrated by actual improvement in tubal pregnancy and function during prolonged or repeated insufflation as recorded on the kymograph, and by pregnancy which follows soon thereafter. As many as 18 tests may be performed before pronouncing a patient as hopeless.

**Treatment of Functional Sterility.**—In considering the treatment of functional sterility, it is of course clear that prophylaxis in the adolescent youth is of the utmost importance. A large number of functionally sterile women cite a history suggestive of glandular disturbance in early adolescence. The resulting incomplete development of the genital organs should, therefore, be guarded against at this period in order to avoid the possibility of sterility in later life. All endocrine disorders should be treated at once. It is indeed unfortunate if initial complaints referable to a disturbed genital physiology are ignored.

*Optimal Time of Conception.*—Too frequent intercourse may empty the epididymis of sperms before they are ripened and thus cause sterility.

Recently, renewed interest has been manifested in the age-old question as to the most favorable period of impregnation. Generally speaking, one may say that conception is most frequent after coitus following ovulation. Sterility, therefore, may be due in some cases to the fact that coitus occurs only during the period of "physiologic sterility." If a woman menstruates every twenty-eight to thirty days, conception is most likely to take place between the eleventh and seventeenth day after the beginning of the period. If she has a cycle of forty days, her most fertile period is fourteen days before the expected flow.

*Organotherapy.*—Despite the noteworthy advance made in the manifold aspects of endocrinology, organotherapy until quite recently was almost void of accomplishment. In all instances the correction of menstrual irregularities is of vital importance in the treatment of functional sterility.

*A. Thyroid.*—This is a most valuable adjuvant in the treatment of functional sterility and may be used even when

the basal metabolism is normal or slightly subnormal. The administration of desiccated thyroid tissues,  $1\frac{1}{2}$  or 2 grains (0.09 or 0.13 Gm.) daily, tends to increase cellular activity throughout the entire body, including the endocrine glands. In addition, it has been shown that thyroid neutralizes the effects of estrogenic substance on the endometrium, which may explain the temporary beneficial effects of thyroid therapy in functional uterine bleeding when prolonged and unantagonized action of estrogenic substance on the endometrium is the immediate cause of abnormal bleeding itself.

B. *Estrogenic Substance*.—It must be remembered that, despite restoration of pituitary function, the marked uterine atrophy, either primary or as a result of a preexisting pituitary deficiency, may in itself become the cause of the continued amenorrhea and sterility. Estrogenic substance has no effect on the ovary, but it does evoke an increase in growth and vascularity of the uterus and renders it, therefore, more responsive to improved or normal ovarian stimulation.

It has been determined by Mazer that 1000 rat units administered hypodermically every third day or 1000 rat units orally, in three divided doses daily, will maintain the normal estrogenic level in the castrated woman. This high dosage, however, is not required in the ordinary case of sterility, because in these patients there is actually some degree of ovarian function. It becomes necessary, therefore, to determine the excretion of estrogenic substance in the urine and blood and, if below normal, to administer an amount sufficient to maintain a normal level of daily urinary excretion. A woman who shows one half of the normal level of estrogenic substance should receive only one half of the full therapeutic dose.

C. *Anterior Pituitary-like Gonadotropic Hormone*.—The administration of anterior pituitary-like gonadotropic substance in 200 rat units combined with anterior pituitary lobe extract, 2 cc. given every other day for ten weeks, may increase the fertility index. It is moderately successful in irregularly menstruating women in stimulating luteinization and in creating an endometrium favorable for nidation.

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D. *Insulin*.—This preparation employed in a dose of 10 units administered one-half hour before breakfast and dinner is chiefly effective in cases of primary ovarian failure. Not only is body weight increased, but distinct improvement in genital function is noted.

*Irradiation*.—Low dosage irradiation of the pituitary gland and ovaries affords the best results in the treatment of menstrual disturbances with functional sterility associated. Strict adherence to all the technic laid down by the roentgenologist is most essential, *i. e.*, from 50 to 80 roentgen units or from 7.5 to 12.5 per cent skin erythema dose being given once a week over a period of six weeks. The one menstrual disorder which almost invariably fails to respond is hypomenorrhea (scanty flow) in regularly menstruating women. The cause of the menstrual deficiency in these patients is apparently within the uterus itself.

*Surgical Treatment*.—Lacerations of the vaginal wall and cervix, if present, should be corrected. In acute ante flexion of the uterus, dilatation and curettement, and occasionally the introduction of an intra-uterine pessary or drain, may do some good. Repeated dilatation of the cervix and curettage of the endocervical mucosa will probably cure some cases. Incision of the posterior lip of the cervix with removal of a small wedge of cervical tissue to facilitate drainage, may be helpful. Linear cauterization of the cervix is of value in chronic endocervicitis. Displacements of the uterus, if uncomplicated, should be corrected by manual or mechanical means. If complicated, operation should be resorted to. If benign tumors are present and thought to be responsible, these naturally should be removed.

If investigation reveals disorders within the pelvic cavity, especially in the fallopian tubes, the advisability of operation should be considered.

Uterosalingography is advisable only prior to contemplated operation. Fifty per cent neoskiodan in distilled water is employed as the radiopaque medium. If the uterine ends of the tubes are obstructed bilaterally, operation is hopeless. On the

other hand, if the fimbriated ends are obstructed, operation may be attempted.

However, tubal conditions are usually of an inflammatory nature, and, while tubal disorders may be overcome by re-opening the fimbriated ends, by attempting a restoration of the tubal canal, or by manufacturing new ostia (salpingostomy), the final results have been so unsatisfactory as to hardly justify the means. After salpingostomy in selected cases the tubes should be tested with gas or iodized oil at intervals to prove that they remain open. Gross inflammatory lesions of the tubes are usually permanent and from a practical standpoint functional restoration of these structures is impossible, and hence conception, following operation of whatever nature on these organs, is very improbable.

Surgery of the ovaries in which follicle cysts are ruptured may be of value.

Finally, one can hold out a hope for cure in sterile marriages in 50 per cent of cases where the tubes are patent and the male has some degree of fertility.



## CONTRIBUTION BY DR. NORRIS W. VAUX

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### DIAGNOSTIC MISTAKES IN GYNECOLOGY

No one is more qualified to undertake writing an article dealing with the diagnostic mistakes in gynecology than I, and if there are any errors to which the human may fall heir, that I have not made, I would be extremely interested in knowing what they are. Experience is a hard teacher and one that leaves a vivid imprint of our errors, with their possible corrections, staring down at us from the walls and memories of the past. With this in mind, I shall briefly set down herewith a few words from my experience, which may help others to avoid some of the more common diagnostic errors by keeping before them the fundamental principles of the medical art. The usual diagnostic errors are ones in which, for the most part, the simple rudiments of physiology and anatomy and physical diagnosis are discarded for the more scientific and recent advances in laboratory technic and tests which have, it appears, taken their place in the practical and clinical experiences of others in large institutions and in teaching schools. Through the aid of the biological tests we are no longer dependent entirely upon the subjective and objective signs and symptoms of pregnancy to make our diagnosis. However, if one is mindful of the physiological changes occurring, and proceeds in making the diagnosis on the clinical findings established in the individual, it is seldom necessary to resort to the biological tests of Friedman-Lapham and Aschheim-Zondek. Pregnancy occurring in an individual who already has a complicated pelvic pathology such as ovarian cyst, myoma uteri, pelvic adhesions, etc., is frequently confused and the diagnosis of pregnancy often overlooked. It is in these



rather complicated diagnoses that we should be aided by the biological tests of pregnancy along with the clinical findings and diagnosis. The history of the individual such as abnormal amenorrhea which occurs occasionally in those suffering from endocrine deficiency, is seldom given the proper amount of importance. The whole problem of endocrinology can be held in close relation to the female pelvic organs and where the clinical history and study fails to throw light upon the individual problem confronted, a further and more intense endocrine study should be instituted. Although diagnostic errors are frequently made in determining the etiological factor of amenorrhea, a word of caution relative to the prolific use of endocrine substances to right this deficiency is timely. One should be opposed to the often widespread misuse of any or all of the endocrine substances, without first making a complete and careful clinical study with full laboratory analysis of the individual's blood to determine which of the endocrine substances, if any, is a possible potential factor needed in the individual case of amenorrhea. The cause of a large proportion of potential sterility cases lies in the failure of the endocrine substances to produce a normal premenstrual endometrium, which can at times be artificially produced. Certain individuals normal in all other respects, being mated with a fertile mate, will not become pregnant until a healthy premenstrual endometrium is present. In these cases it is essential, therefore, that a proper curettement and study of the endometrial tissue removed, be made before positive diagnosis of endocrine deficiency and lack of corpus luteum stimulation be given as the etiological factor.

**Abortions and Miscarriages.**—Diagnostic mistakes are common in this all too common interruption of early pregnancy. The diagnosis of pregnancy must be established first. As to whether the abortion or miscarriage is threatened or inevitable, remains to be determined on a clinical basis. A moderate amount of bleeding at the menstrual epoch does not always mean an inevitable abortion or miscarriage, but the passing of decidual tissue and embryological products deter-

mined by macroscopic and microscopic examination with a differential between the threatened and the inevitable types. The more severe the bleeding and pain, the more guarded the prognosis should be and the more likely it is that the threatening termination will become inevitable. Excessive bleeding and uterine cramps with a moderate dilatation of the cervix and bulging of the lower uterine segment, place the case in the category of inevitable. Vaginal examinations are to be curtailed during the period of bleeding, as often this examination may add sufficient irritation to cause what is only threatening, to become inevitable. Intercourse during pregnancy, relatively near the menstrual epoch, is not given sufficient significance as a causative factor, and neglect in instructing the individuals to this effect is the physician's responsibility.

#### **Ectopic Pregnancy and Pelvic Inflammatory Disease.**

—The making of a differential diagnosis between ectopic pregnancy and pelvic or adnexal tumor masses is very difficult, and errors in establishing the correct conclusion are frequent. The history of previous infection is important, and if time permits, sedimentation test and a study of the clinical cause of the abnormality will help materially in reaching a diagnosis. The negative biological pregnancy tests as well as the leukocytosis which is present in the pelvic inflammatory cases, are of decided benefit. The adnexal masses associated with pelvic inflammatory disease are usually bilateral, while a bilateral tubal pregnancy is very rare. The pain and tenderness in the inflammatory cases is not as definitely localized as is the tenderness and local pain over the tube affected in ectopic pregnancy. On abdominal palpation the tenderness and rigidity in pelvic inflammatory disease is usually bilateral and lower abdominal, while in ectopic gestation this can only be elicited clinically when the tubal leak or rupture has taken place, with the subsequent increase in the peritoneal irritation and associated high leukocytosis which accompanies the presence of blood in the abdominal cavity. A posterior cul-de-sac puncture is advisable in all doubtful cases and is often helpful in making the diagnosis of tubal leak or rupture by the presence

of blood in the peritoneal cavity, while a cul-de-sac puncture free of blood would indicate more readily the presence of tubal and pelvic inflammatory disease. The diagnosis in carcinoma of the cervix has long been a frequent stumbling block of diagnostic error in this branch of gynecological practice. All cervixes should be carefully inspected as well as palpated, and the parametrial tissue and condition of the pelvic organs noted. The Schiller test and colposcopy examinations of erosions, ulcerations and eversions of the cervical mucosa and tissue are all to be looked upon with suspicion of malignancy until a further careful biopsy study is made of the removed tissue involved, which will either confirm or disprove your suspicion. The only positive method of diagnosing early malignant disease of the cervix is the careful pathological study of the removed tissue, which portion must include that area or areas of the cervix which are suspicious as to their appearance, and those areas which show definite reaction to the Schiller test. Endometrial scrapings which resemble malignancy are often erroneously diagnosed, and as this fatal complication can be completely arrested or cured in the early stages, drastic and intensive efforts should be made to prove or disprove the presence of early malignancy. No bleeding cervix should go undiagnosed or be allowed to continue with local applications alone. The immediate removal of the suspected tissue for study and diagnosis is the only correct method of preventing this diagnostic error. The diagnosis of malignancy cannot always be positively made without a thorough pathological study of the tissue, which study may have to be repeated, if the clinical manifestations persist. All examinations of the pelvic organs should be made wherever and whenever possible, with the bowels and bladder empty, preferably on a table in a proper gynecological lithotomy position, with sufficient light to justify a clear vision of the cervical and upper vaginal field. Neglect of this important procedure has frequently been responsible for inaccurate diagnoses of pelvic tumors and masses erroneously palpated and considered present. Cervical polyps should never be removed without includ-

ing their bases and a wide area of the surrounding tissue, and a complete pathological study made of the same. Polyps may be, or become malignant in character. Vaginal bleeding should not deter a proper gynecological examination. It is occasionally better and more advisable to have a clear conception of where the bleeding is coming from, and this can be accomplished only by visualization of the area. By no means should the examination be postponed indefinitely because of the bleeding alone. Every woman who has postmenopausal bleeding is a subject for complete and thorough investigation of first, the general systemic condition, and second, the pelvic organs, with malignancy always uppermost in our mind. If we postpone or neglect this important incipient stage, grave error is the result. Metrorrhagia is at times significant and diagnostic of some abnormality, the character of which is to be determined.

**Malpositions of the Uterus.**—The malpositions of the uterus are a source of much diagnostic controversy. The presence of uterine and adnexal malpositions is frequently confused with digestive, urinary and nervous conditions. Before a correct and accurate diagnosis can be made, the retroflexioversions, prolapse of the ovary, and acute antelexions must be corrected by manipulation or surgical procedure. The common complaint of patients with backache is never fully and completely gone into to the extent of determining the etiological factor, and errors in diagnosis result. The pelvic organs are frequently said to be the cause, when postural position, gastropptosis and allied genito-urinary and intestinal factors play the chief rôle in sacral and low lumbar irritability. Whenever possible, and always previous to the preparation of the patient for plastic and abdominal operation, the operator should make a complete check-up of his diagnosis with the patient under anesthesia, to avoid carrying out unnecessary and often harmful operative procedures. The recent work of Dr. Taylor on the influence of endocrine substances on a painful breast is timely and well considered, yet not any of the tumors of the breast, be they cystic adenoma

or malignant, should remain unstudied and untreated. Errors in diagnosis are common when a cystic mastitis is given as the diagnosis while malignancy exists in the tissue involved. Pathological examination of all tissues removed for diagnosis is timely and every tumor of the breast should be excised and carefully studied before a major procedure is undertaken. Neglected x-rays of the chest in suspected malignant tumors of the breast are frequently the cause of diagnostic errors in that metastasis can be noted in the lung tissue before symptoms are evidenced. No contemplated radical operation on the breast should be considered without a complete and thorough x-ray study of the mediastinal and pulmonary areas. Some of the painful breasts can be controlled well with a specific endocrine substance but the error lies in attempting to control the discomfort of the patient by the use of those simple, yet at times harmful hypodermic medications, while a malignancy is continuing its rapid proliferation into the adjacent glandular tissues and adjacent lymphatic structures.

**Vaginal Discharges.**—Probably more errors are made in diagnosing and treating vaginal discharge than all other gynecological complications. First, it is important to have the vaginal, cervical and urethral smears made from the discharge and these to be examined in the fresh state or in a hanging-drop as the presence of *trichomonas vaginalis* is frequently overlooked, if the fresh smear is not so examined. Other discharges must be stained and a routine search made in the specimen for the presence of *diplococcus* of Neisser, *streptococcus*, *bacillus* of Doederlein and significance for the treatment placed on the predominating organism found. Most of these conditions can be corrected; a large number cured; and a certain percentage remain unchanged after the proper treatment is instituted for each individual case. All ulcerations and erosions of the cervix and cervical canal must be treated by the cautery. On numerous occasions it will be necessary to remove the cervix and the cervical endometrium to completely arrest this distressing and common complaint in women. Too frequent douching is to be decried and it is desirable to

refrain from the use of too strong and irritating substances in the douch material. A cleansing alkaline douche, mild in type, will often give more satisfactory results. The patient should be instructed that the chronic types of leukorrheal discharge are difficult to cure and must persist in the treatment over a long period of time, to have a successful termination of the difficulties. Most of the irritating discharges will recur unless the positive etiology is determined and treatment directed toward its elimination.

**Persistent Abortions and Miscarriages.**—Persistent abortions and miscarriages are not uncommon in certain individuals and treatment can be directed toward the elimination of the abnormalities which may exist in the female organs of reproduction. Recently it has been determined by some investigators that a proportion of these individuals can be carried successfully to term by the use of "proluton." Distinct error is often brought about by the injudicious advice given individuals who are suffering from repeated disappointment due to this abnormality. The consequences are that the individuals themselves consider their case hopeless and their idea of a successful issue is abandoned. A word of caution will save serious error brought about occasionally by the injudicious cauterization of the cervix in child-bearing women. Conization and cauterization of the cervix are not procedures for the general practitioner and the reproduction of the individual must not be lost track of, as improperly performed cauterization will cause cicatricial stenosis of the cervix which may ultimately result in dystocia in the first stage of labor. It is further to be cautioned that an extensive conization of the cervix is not to be considered as a dispensary or an office practice, for the reason that severe hemorrhage can, and will follow such procedure if the patient is not kept in bed under observation for a forty-eight-hour period following this extensive procedure.



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### THE CAUSES OF ABNORMAL VAGINAL BLEEDING DURING THE PRE- AND POSTMENOPAUSAL AGES

THE menstrual lives of woman may be divided into four periods, each of which is accompanied by characteristic peculiarities of menstruation and by more or less characteristic pathologic conditions which result in abnormal bleeding. During the adolescent period, while the rhythm of the cycle is being established, disturbances in endocrine function give rise to most of the menstrual abnormalities. The child-bearing period is accompanied occasionally by dysfunctional bleeding, but those conditions which result from sex lives, genital infections and abnormalities of pregnancy, predominate as the causes of abnormal bleeding. In the premenopausal age, gradual recession of ovarian function is attended frequently by functional menstrual disturbances, but doubly as frequent are the neoplastic diseases, both benign and malignant, which characteristically appear at this time. During the postmenopausal era any vaginal bleeding is pathological in origin. Such bleeding usually depends upon local atrophic changes incident to the menopause or follows the development of neoplastic disease.

The study of irregular pre- and postmenopausal bleeding is particularly important because of the frequency with which malignancy occurs during these ages. The menopause theoretically is that point at which ovarian function ceases and permanent amenorrhea appears. Clinically, however, it is often impossible to designate such a point. The average age of the



menopause was found by Dr. Charles C. Norris to be forty-seven and one-half years (Fig. 1). The age limits extended from forty to fifty-five years, with a gradual rise in incidence from forty to forty-eight years, and a sharp decline after forty-eight years.

The length of the premenopausal era ranges from a few months to several years, during which time irregularities of menstruation frequently occur. It is often difficult to interpret correctly these irregularities because of the wide variations both in interval and in character of the flow which commonly

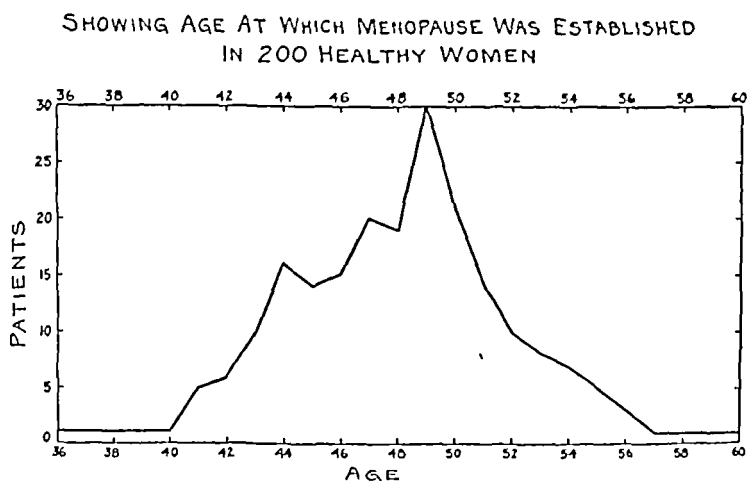


Fig. 1.—(Norris in *International Clinics*, vol. I, Series 45. J. B. Lippincott Co., Publishers.)

accompany the normal change of life. While they usually indicate simple functional disturbances, the possibility of more serious conditions should always be borne in mind. Particularly is this true in the event of bleeding between the regular menstrual periods.

Many of the figures in this article are based upon a study of 2000 patients forty years of age or over which has been reported by Dr. Floyd E. Keene elsewhere, to whom the author is grateful for permission to use his statistics. The patients are divided into the premenopausal group of 1398 patients and the postmenopausal group of 602.

**Premenopausal Bleeding.**—The conditions which resulted in abnormal bleeding during this period were benign in practically 86 per cent of the cases and in the remaining 14 per cent malignant disease was responsible (Table I). The

TABLE I  
PREMENOPAUSAL HEMORRHAGE—1398 PATIENTS

Benign lesions	86.4 per cent
Malignant lesions	13.6 " "

*Organs Involved*

	<i>Benign</i>	<i>Malignant</i>
Uterine body	64.8 per cent	15.2 per cent
Tubes and ovaries	28.7 " "	5.8 " "
Cervix	5.9 " "	76.4 " "
Vagina or vulva	0.3 " "	2.6 " "
Systemic diseases	0.3 " "	0.0 " "

locations of the lesions are interesting when the benign and malignant conditions are contrasted. Over 90 per cent of the benign conditions occurred in the upper genital tract, while 80 per cent of the malignant diseases were found in the lower tract. Cervical cancer accounted for more than 75 per cent of the malignant bleeding, and less than 6 per cent of the benign bleeding could be attributed to cervical conditions. While fundal malignancy is usually a postmenopausal condition, the 15 per cent incidence here recorded shows that it should always be considered in the absence of other obvious lesions to account for irregular bleeding.

Of the benign conditions which caused abnormal premenopausal bleeding, tumors made up two thirds of the group (Table II). Uterine myomata were by far the most fre-

TABLE II  
PREMENOPAUSAL HEMORRHAGE  
*Types of Benign Lesions*

Tumors	66.0 per cent
Inflammation	4.1 " "
Pregnancy	2.9 " "
Trauma	1.2 " "
Dysfunction	25.5 " "
Systemic diseases	0.3 " "

quent and they comprised over 60 per cent of all the benign lesions. Endometrial and cervical polyps were moderately common and ovarian tumors accounted for a small number. Ovarian dysfunction caused one fourth of the irregularities. Functional menstrual disturbances are most likely to occur at this age. In a recent study of functional uterine hemorrhage, we found that one half of the cases fell between the ages of forty and fifty years. The progressive ovarian changes which eventuate in the menopause, frequently result in abnormal secretion, distorted endometrial stimulation and irregular bleeding. In many instances such irregularities do not cause concern unless excessive blood loss results. The occurrence of bleeding between the menstrual periods, however, should always suggest the possibility of malignant disease. Genital infections and complications of pregnancy play a very small rôle during the premenopause. The inflammatory group in Table II is composed of vaginal ulcers, cervicitis and cervical erosions with infection, as well as adnexal inflammatory lesions. Pelvic inflammatory disease contributed less than 2 per cent of the causes of benign irregular bleeding in this study. Benign cervical lesions likewise accounted for less than 2 per cent of the abnormal bleeding. The fact that this study was based upon hospital patients may produce a distorted picture of the true incidence of bleeding benign cervical erosions. Yet we cannot escape the conclusion that, as Dr. Keene puts it, "in a woman of the menopausal age an erosion of the cervix which bleeds is often malignant." The curability of cervical cancer is inversely proportionate to the stage of its extension, and early diagnosis is certainly the most important factor in its successful management. Because of its location in an area which is practically devoid of sensory nerve fibers, pain does not occur until the growth has become hopelessly advanced. The most frequent symptom of early cervical cancer is irregular vaginal spotting from an area which bleeds following trauma.

Among the recently proposed methods of rapid diagnosis of cervical malignancy are the Schiller test and the use of the

colposcope. The Schiller test is based upon the fact that malignant cells, because of the lack of glycogen, do not take the iodine stain. While we have found this procedure to be valuable in locating questionable lesions for the purpose of biopsy, it does not enable final diagnosis. Our experience with the colposcope has not induced us to employ it to the exclusion of the final and most important diagnostic procedure: biopsy of the suspicious areas and microscopic study of stained sections by one who has been trained in gynecologic pathology. This examination is indicated in the presence of any cervical erosion occurring during the premenopausal age, which bleeds upon trauma.

Approximately three fourths of the menstrual irregularities of the premenopause arise from either the cervix or the body of the uterus. Comparison of the relative incidence of benign and malignant lesions in the two sites shows that over 65 per cent of the cervical and less than 4 per cent of the fundal lesions were malignant (Table III). Abnormal premenopausal

TABLE III

## PREMENOPAUSAL HEMORRHAGE

*Relative Incidence of Benign and Malignant Uterine Lesions*

	<i>Benign</i>	<i>Malignant</i>
Cervix .....	32.7 per cent	67.3 per cent
Body .....	96.4 " "	3.6 " "

bleeding of cervical origin is usually due to cancer, while similar fundal bleeding is usually benign in origin. The fact that 4 per cent of the fundal lesions were malignant, emphasizes the importance of careful investigation of the endometrial cavity. Most of the cases of unsuspected fundal cancer which have been found in our laboratory occurred in association with myomata. Approximately 1 per cent of the myomata undergo sarcomatous degeneration. Adenomyomata in rare instances became carcinomatous. A greater possibility is that an endometrial cancer may be masked by the presence of a myoma. The characteristic menstrual abnormality of the uncomplicated uterine myoma is menorrhagia (profuse or prolonged bleeding

at the regular menstrual time). In the event of metrorrhagia (intermenstrual bleeding), the existence of some complicating condition, such as a pedunculated, submucous tumor, endometrial polyps, benign or malignant degeneration of a myoma, or a malignant endometrial change should always be suspected.

**Postmenopausal Bleeding.**—Because of the great difficulty in determining accurately the exact time of the menopause, no patient was included in the postmenopausal group unless a year or more had elapsed between the last menstrual period and the development of irregular bleeding. The menopause is accompanied by changes in physiology and in the pelvic structures, which alter the types of conditions responsible for vaginal bleeding. During the premenopause, a considerable proportion of the menstrual abnormalities, both in the presence of myomata and otherwise, result from disturbances in ovarian function. On the other hand, postmenopausal bleeding usually follows some form of degeneration, either benign or malignant. In fact its occurrence is due to malignancy in approximately 60 per cent of the cases (Table IV).

TABLE IV  
POSTMENOPAUSAL HEMORRHIAGE  
*Incidence of Malignant Causes*

<i>Author</i>	<i>No. Pts.</i>	<i>Malignancy</i>
P. T. Brown	164	66.8 per cent
H. C. Taylor, Jr.	298	63.0 " "
F. E. Keene	602	61.4 " "
Geist and Matus	190	58.0 " "
C. C. Norris	189	52.9 " "
Total . . . . .	1443	60.7 per cent

In the series reported by Dr. Keene, benign lesions accounted for only 38 per cent of the postmenopausal bleeding (Table V). These nonmalignant lesions were situated in the lower genital tract in more than three fourths of the cases. The atrophic uterus accounted for about 15 per cent of the benign postmenopausal bleeding, against the overwhelming preponderance of 65 per cent which is seen in the premenopause. On

TABLE V

## POSTMENOPAUSAL HEMORRHAGE—692 PATIENTS

Benign lesions .....	38.6 per cent
Malignant lesions .....	61.4 " "

*Organs Involved*

	<i>Benign</i>	<i>Malignant</i>
Uterine body .....	16.7 per cent	39.6 per cent
Tubes and ovaries .....	2.1 " "	3.0 " "
Cervix .....	58.5 " "	53.3 " "
Vagina or vulva .....	20.1 " "	4.1 " "
Unexplained .....	2.6 " "	0.0 " "

the other hand, the uterine fundus housed 40 per cent of the malignant conditions causing postmenopausal bleeding, most of which were fundal cancer. It is interesting to note that even after the menopause, cervical malignancy is much more frequent than malignancy of the fundus.

The benign lesions which resulted in postmenopausal bleeding were neoplastic in only 40 per cent of the cases (Table VI). These lesions consisted of endometrial or cervical

TABLE VI

## POSTMENOPAUSAL HEMORRHAGE

*Types of Benign Lesions*

Tumors .....	40.3 per cent
Inflammation .....	29.6 " "
Trauma .....	27.5 " "
Unexplained .....	2.6 " "

polyps, myomata and a small number of ovarian cysts. Polyps cause postmenopausal bleeding far more frequently than do myomata. The postmenopausal fibroid is a heritage from the menstrual era, and bleeding from this source usually indicates benign or malignant degeneration of the tumor or an associated malignancy either in the endometrium or adnexa.

The atrophic genital changes incident to the cessation of ovarian function form the basis for almost all the remaining benign postmenopausal bleeding. The thinned out ischemic tissues of the lower genital tract are particularly susceptible to nonspecific infection and to trauma. Senile vaginitis is com-

monly accompanied by multiple small areas of ecchymosis which cause irregular spotting. The postmenopausal prolapsed urethral mucous membrane often bleeds on trauma. The atrophic cervix occasionally presents a bleeding erosion. Frequent causes of spotting are the cervical and vaginal ulcers which accompany varying degrees of postmenopausal uterine prolapsus.

Therefore, trauma and infection, or a combination of the two, accounts for approximately 60 per cent of the benign postmenopausal bleeding. The bleeding which accompanies these conditions is usually scanty, often no more than blood-stained leukorrhea. The importance of these lesions lies in the fact that they may mask the presence of more serious trouble. The character of the discharge or bleeding and the duration of symptoms often aid in the decision as to the necessity for thorough investigation. If the examination can be made at the time of bleeding, the origin of the blood is usually determined. Any postmenopausal bleeding from the uterine fundus, either spontaneous or following trauma of the endometrium with the sterile sound, indicates an immediate diagnostic curettage. In the absence of this posttraumatic uterine bleeding and in the presence of an obvious cause for the spotting in the lower genital canal, as vaginitis, cervical polyps, etc., it is generally safe to treat these conditions and to keep the patient under careful observation for at least a year. Should the bleeding persist after the obvious lesions are cleared up, or should it recur, the endometrial cavity must be investigated at once. A small area of uterine malignancy may escape even a thorough curettage. Pemberton recently reported 6 cases of fundal carcinoma, from a group of 923 patients, which developed in such a short time after the curettage that he believes they were missed by the curet. We have not had a similar experience but in approximately 3 per cent of our postmenopausal hemorrhages, thorough examination including curettage under anesthesia has not revealed the cause of the bleeding. Postmenopausal rejuvenation occasionally occurs, with the appearance of pseudomenstruation. At times no

reason is found, and occasionally it is the result of ovarian cancer. Particularly is this true of granulosa cell tumors of the ovary, which secrete estrin and stimulate endometrial changes similar to those found in many instances of dysfunctional uterine bleeding of the menstrual era.

TABLE VII

## POSTMENOPAUSAL HEMORRHAGE

*Relative Incidence of Benign and Malignant Uterine Lesions*

	<i>Benign</i>	<i>Malignant</i>
Cervix . . . . .	40.8 per cent	59.2 per cent
Body . . . . .	21.1 " "	78.9 " "

The uterine cervix and the fundus proved to be the cause of bleeding in approximately 80 per cent of all the cases of postmenopausal hemorrhage. Of the cervical lesions, 40 per cent were not malignant and consisted mostly of benign polyps and those conditions resulting from postmenopausal atrophy plus trauma or infection (Table VII). Of the fundal lesions or when the blood was found to be coming down through a normal cervix, almost 80 per cent of the bleeding was of malignant origin, usually carcinomatous. Given a normal cervix in a woman past the menopause, uterine bleeding usually means cancer.

For the purpose of emphasis, certain salient points are listed below:

Premenopausal abnormal bleeding is malignant in origin one out of six times, while postmenopausal bleeding is malignant four out of six times.

Premenopausal cervical bleeding, in hospital cases, is malignant two out of three times, and premenopausal fundal bleeding is malignant one out of twenty times.

Postmenopausal cervical bleeding is malignant three out of five times, while postmenopausal fundal bleeding is malignant four out of five times.

Premenopausal menorrhagia is usually benign in origin, but metrorrhagia at this age is always suggestive of malignancy.



Postmenopausal bleeding in most instances arises from degenerative lesions, 60 per cent of which are malignant.

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### TREATMENT OF HABITUAL ABORTION

HABITUAL abortion is a term used to apply to repeated or recurrent abortions in which there appears to be no recognizable cause. Therefore, herein will be considered only those repeated abortions which do not follow the more commonly accepted causes, as infections (lues the most common), abnormal endometrium, decidua and placenta, fibroid growth in the uterus, malpositions, trauma, or defective germ plasm (which may be endocrine).

The problem of habitual abortions is believed by most gynecologists today to be related to an endocrine imbalance, although there is a group who still believe the cause to be hypovitaminosis. The impetus in recent years given to research in sterility studies and endocrinology has added much to the knowledge of the endocrine factor in pregnancy and its premature termination. Habitual abortion therefore has been removed from that discouraging place in medicine allotted to abortion of habit and has been given a very deserving recognition in the study and treatment for relative sterility.

Certain physiological effects of the corpus luteum on the genital tract have been demonstrated and are now accepted. In 1903 Fraenkel<sup>1</sup> proved that the removal of the corpus luteum of early pregnancy in rabbits resulted in the termination of the pregnancy. An interrelationship has likewise been established between the luteal hormone and the fertilized ovum during the early months of pregnancy. Weichert,<sup>2</sup> Allen<sup>3</sup> and others have demonstrated that progesterin, the lutein hormone,

does prepare the endometrium for the fertilized ovum and Hisaw<sup>4</sup> has shown that it exerts an inhibitory influence on the muscular contractions of the uterus. Its ability to inhibit pituitrin has likewise been demonstrated. Other observers have shown that the corpus luteum is necessary for the early months of gestation. Estrin and progesterin are apparently antagonistic in their action upon the uterine musculature.

As a result, the facts have led to the theory that while the corpus luteum is in ascendancy the pregnancy continues, because pituitrin and estrin are inhibited. If estrin becomes dominant the uterus is sensitized to pituitrin and labor ensues.

As early as 1913 Seitz<sup>5</sup> suggested the corpus luteum as the cause for pathologic changes in habitual abortions. In 1919 J. C. Hirst<sup>6</sup> used an aqueous extract of corpora lutea obtained from pregnant cattle in attempting to prevent abortions. Hofbauer,<sup>7</sup> Halban,<sup>8</sup> Glismann,<sup>9</sup> Schwarz,<sup>10</sup> Kunz,<sup>11</sup> Mazer and Goldstein,<sup>12</sup> Wells,<sup>13</sup> Hall,<sup>14</sup> Bishop<sup>15</sup> and others have treated habitual abortions with some preparations of progesterin. Witherspoon<sup>16</sup> has used the anterior pituitary luteinizing hormone in abortions with such satisfactory results and suggests the use prophylactically in cases of habitual abortion, follutein was used. Sellheim<sup>17</sup> used the blood serum from normal, healthy pregnant women to treat nine patients who had previously aborted two or three times between the third and fourth months. He used 10 cc. of blood serum every two weeks with satisfactory results.

An indirect endocrine imbalance is apparently due to thyroid deficiency. Roffo,<sup>18</sup> Bland,<sup>19</sup> von der Hoeven,<sup>20</sup> LeLorier<sup>21</sup> and M. Mayer and others believe that thyroid deficiency is responsible for sterility and if pregnancy ensues will cause abortion in later months if not treated. They report excellent results on thyroid therapy in those cases showing deficiency prior to pregnancy and in those cases especially which abort in the late months of pregnancy.

Carbohydrate metabolic imbalance either existing before as diabetes or during pregnancy has been treated by low

carbohydrate diet and insulin with success. Williams<sup>22</sup> in a series of 19 cases found a very low sugar tolerance and advised reduction of total carbohydrate intake, about 150–200 Gm. a day, taken in small rations at more frequent intervals. In 2 cases he used insulin.

Hypovitaminosis must be considered. Much has been written on deficiency in vitamin E in sterility and in causing habitual abortions. Vogt-Möller<sup>23</sup> has probably contributed more than any other on the use of wheat germ oil or wheat germ in treatment of abortions. He suggests that the vitamin E content of an ordinary diet is difficult to estimate and, too, that some women require more than the ordinary amount of vitamin E. He also believes that a hypovitaminic state exists during pregnancy caused by the increase in the maternal metabolism and vitamin requirement of the fetus. He further asserts that this may reflect back to the thyroid imbalance, dental caries, anemia, neuritis, etc. Since wheat germ oil is entirely harmless he believes all cases should be treated with it. He gives 5 cc. wheat germ oil daily by hypodermic, in early pregnancy, for two weeks, and gradually decreases to 5 cc. every six days until the patient has passed the time for the abortion to occur.

**Treatment.**—Habitual abortions appear to be explained physiologically and since the causes relate to a disturbance of the secretion of the ovarian hormones, treatment lies in the adjustment of the quantitative relation of estrin and progestin. The therapy, therefore, is prophylactic and consists in general or constitutional and specific or endocrine treatments.

**Constitutional.**—*Tonic.*—The same general tonic treatment necessary in all prenatal cases is especially required. Attention should be given to the intake of cod liver oil, calcium, iron, etc.

**Dietetic.**—A well-balanced diet with preponderance of green vegetables and fruits, together with 1 quart of milk daily must be assured. Variations are applicable for individual indications as in other prenatal cases. Carbohydrate metabolism must be watched, using blood sugar estimations

to control carbohydrate intake. Experimentally, deficiency in vitamin E has been responsible for repeated abortions but this has not been proved the case with humans. However, it must be borne in mind in cases not responding to other treatment.

*Sedative.*—Rest has proved in my experience a very helpful method in preventing termination of pregnancy prematurely. At the time of the menstrual date the patient is kept in bed for two days prior and during the time corresponding to the usual menstruation period. Coitus is forbidden at any time. No automobile rides at any time. Strenuous activity of all kinds is removed. If there are no threatening symptoms, walking is the one exercise approved. Keep bowels moving normally with mineral oil and laxative foods, avoiding laxative drugs in order to maintain a physiological rest of the intestinal tract. In some cases sedation is necessary; using bromides, opiates are reserved for cases showing symptoms of abortion.

**Endocrine Treatment.**—*Substitutive.*—Without doubt, the best results are obtained in the prevention of habitual abortions in the early months by the use of corpus luteum (progestin). One cc. ampule containing 1 rabbit unit of luteum hormone should be given two or three times a week, intramuscularly until the fetus is viable. Some clinicians give it only during early months. Krohn<sup>24</sup> gives the medication until after the thirty-second week and permits his patients to be ambulatory unless abortion symptoms arise.

*Stimulative.*—The increased functional activity of the thyroid during pregnancy is a known observation and it is logical to assume that it does participate in the changes taking place within the uterine mucosa of pregnancy. There are those cases in which the thyroid seems unable to meet the demands. It is in these cases that thyroid glandular extract is indicated. The dosage should be regulated by the pulse rate and basal metabolic rate. There are clinicians who recommend its use even without apparent cause. Bland<sup>19</sup> employs 1½ grains daily for one week, alternating with 10 grains

sodium iodide. Mazer<sup>12</sup> gives 2 ampules of corpus luteum extract subcutaneously every other day for the first twenty days of each month until the fetus is viable. He also gives  $\frac{1}{2}$  grain desiccated thyroid for two weeks and 4 grains of sodium iodide the other two weeks, alternating during this same period.

There is much contradictory evidence concerning the results from the use of the anterior pituitary sex hormone in treatment of habitual abortion. My own experience does not warrant the use because, although theoretically it stimulates the corpus luteum, it likewise stimulates the production of estrin, which is antagonistic to pregnancy. The author has had no experience with blood serum but feels that the same objection applies.

**Summary.**—Substitutional treatment with the lutein hormone appears to be the logical and clinically proved effective treatment for habitual abortions. The use of thyroid medication alternating with iodides has been clinically valuable especially in cases showing thyroid deficiency and in those cases aborting in the latter months of pregnancy. Active endocrine therapy must be used prophylactically and not discontinued even when abortion is threatened until the fetus is definitely no longer viable. Tonic, dietetic and sedative measures are additional adjuncts and are not to be overlooked because, in the author's experience, meticulous attention to minor details have in her opinion made possible many good results.

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## CLINIC OF DR. AARON CAPPER

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## THE DIAGNOSIS AND TREATMENT OF CYANOSIS OF THE NEWBORN

**Introductory Remarks.**—In discussing cyanosis of the newborn, one must include as well, for the sake of completeness, a discussion of asphyxia of the newborn. The latter condition is the broader concept and includes as its etiologic agent or agents, many of the causes of cyanosis. The pathologic changes that are present in the blood of cyanotic infants are also a predominant feature of asphyxia. Most cases of asphyxia neonatorum exhibit cyanosis as one of the signs. The term "asphyxia" is usually employed to describe that condition in which spontaneous respiration is not established with sufficient promptness or force to maintain life. It follows, therefore, that when respiration is established, asphyxia no longer exists. Cyanosis, however, may and does continue for many hours, days, weeks, months and even years after normal respiration has been instituted.

The placenta is the medium through which fetal respiration is carried on in utero. It is through this organ that oxygen is received and carbon dioxide carried off. When the placental circulation is suddenly interrupted, the supply of oxygen is suddenly cut off and carbon dioxide accumulates in the blood. It is presumed that as a result of the accumulation of carbon dioxide, an increase in the hydrogen ion concentration of the blood develops, which, in turn, is the initial stimulus to the respiratory center. The greatest immediate danger which the



newborn encounters on its way into the world, is the interruption of its intra-uterine respiratory mechanism. Every baby is, as a rule, born with some degree of asphyxia. This is produced in utero by the uterine contractions, which retard somewhat the placental circulation, thus entailing an increase in carbon dioxide and a decrease of oxygen in the fetal blood. A further intensifying of the already dangerous state is produced by the pressure on the advancing head of the fetus on the pelvic floor, which causes a still greater slowing down of the fetal circulation and hence a decrease in the oxygen content of the tissues. Any factor, therefore, which interferes with placental circulation may produce some degree of asphyxia. The most important of the causes are usually:

1. Prolonged second stage of labor. The likelihood of intra-uterine asphyxia is greater than a direct proportional relationship to the duration of labor, particularly of the second stage. Statistics show that the mortality from asphyxia after a second stage of labor of four hours or more was over three times as great as when it lasted but one hour.

2. The injudicious use of pituitrin.

3. Maternal convulsions.

4. Narcotization, particularly from morphine or nembutal.

5. Breech presentation with difficulty in delivering the after-coming head.

6. Prolapsed cord, pressure on the cord or its wrapping around the neck.

7. Early separation or low implantation of the placenta.

These conditions may cause a cerebral anemia and consequent failure of the respiratory center to function, thus leading to asphyxia or its milder state, cyanosis.

**Definition.**—What is cyanosis? Cyanosis is a bluish discoloration or tinge of the skin and mucous membranes, best observed on the lips, ear lobes and nail beds and, if fairly severe, on any part of the skin or mucous surface. This blueness is caused by an increased amount of reduced hemoglobin in the capillaries of the skin and the mucous membranes. Otherwise expressed, cyanosis develops clinically when a suffi-

cient amount of oxygen unsaturation develops in the blood. Oxygen unsaturation is that value which results when the actual oxygen content of the hemoglobin is subtracted from the oxygen capacity, or it is the difference between the oxygen capacity of the hemoglobin and the actual oxygen carried by it. An oxygen unsaturation of the capillary blood above 6.5 volumes per cent is considered the threshold for the appearance of cyanosis.

**Types or Degrees of Cyanosis.**—Of course, in discussing cyanosis of the newborn, one usually has in mind the generalized form in which the whole skin and mucous membranes appear to be bluish, the depth of the discoloration depending upon the degree of the underlying cause. Often cyanosis is visibly limited only to the lips and nail beds; sometimes it is only circumoral, and then it is usually in its mildest form. Localized cyanosis of one half or only a part of the body of the newborn is usually the result of pressure or constriction of that part during delivery. On the other hand, Smith<sup>1</sup> recently reported three cases of transient localized cyanosis of the newborn following spontaneous delivery, in two of which the face and anterior scalp were involved, and in the third, the head, neck, arms and upper thorax were affected. The cyanosis cleared in all three within five days. In these cases, the author intimated that the cyanosis was undoubtedly the result of interference with free venous drainage of the involved area, due possibly to some vasomotor disturbance of the veins.

Cyanosis is much more common in premature and immature infants, the incidence being at least 50 per cent. Clein,<sup>2</sup> on the basis of postmortem follow-up studies of premature infants, classifies cyanosis into continuous, intermittent, terminal and spontaneous or occasional. The continuous form was present from birth to the time of death and was found to be associated with marked atelectasis of the lungs. Intermittent cyanosis was caused mainly by cerebral hemorrhage, chiefly of the infratentorial type; those infants who died between the tenth and twenty-seventh days of life also had an associated infection. Terminal cyanosis, as the name implies, was pres-



ent a few hours to a day or two before death, and was usually a terminal event in such severe infections as otitis, mastoiditis, pneumonia, tuberculosis or syphilis. Sporadic or occasional cyanosis was seen in a case of congenital heart disease. We do know, however, that occasional cyanosis is not necessarily limited to that cause; on the contrary, congenital heart disease, if it is of the cyanotic type, generally causes continuous cyanosis. Occasionally cyanosis is sometimes encountered in both premature as well as full-term infants, following a vomiting spell, during coughing, gagging, choking and sometimes during feeding.

**Causes of Cyanosis.**—There is quite a variety of pathologic conditions operative in the production of cyanosis of the newborn. Some are mild and easily preventable, others are serious and beyond help. In a general way the causes may be classified as:

1. Those associated with delivery, and the most common are:
  - (a) Aspiration of foreign material.
  - (b) Prolonged and difficult labor.
  - (c) Early placental separation.
  - (d) Cord displacements.
  - (e) Narcotization.
  - (f) Severe circulatory or toxic conditions of the mother.
2. Traumatic conditions of the infant:
  - (a) Cerebral edema.
  - (b) Cerebral hemorrhage.
  - (c) Injury to the phrenic nerve.
3. Developmental anomalies of the infant:
  - (a) Congenital heart disease.
  - (b) Atelectasis of the lungs.
  - (c) Enlarged thymus gland.
  - (d) Diaphragmatic hernia.
  - (e) Prematurity.
  - (f) Micrognathia, leading to tongue swallowing.

## 4. Infectious states of the infant:

(a) Pneumonia or less serious respiratory infections.

(b) Sepsis.

## 5. Metabolic disturbances, especially tetany of the newborn.

While the above list does not exhaust all the possible causes of cyanosis of the newborn, nevertheless, it is believed to account for the great majority of cases in which cyanosis is either the chief symptom or is an important contributory finding. It is most important to bear in mind the possibility of the existence of more than one causative factor in any given case; for instance, a baby that is born with the cord wrapped about its neck may also be the victim of a defect in the heart; an infant with intracranial birth injury may, and frequently does, have an associated atelectasis of the lungs; intracerebral hemorrhage is quite common in premature infants. It is, therefore, incumbent upon the physician not to rest content with the mere finding of one, or even two, distinct pathologic entities, as a possible explanation of the cyanosis, but to thoroughly investigate and study each baby and attempt to exclude every known cause for cyanosis in the course of his differential diagnosis.

**Modus Operandi.**—Some of the pathologic states act directly upon the respiratory center, others interfere with the proper exchange of gases in the lungs; some interfere with the proper entry of air into the lungs, while others do their damage in the circulatory system. The simplest condition is the mechanical obstruction of the larynx and trachea by aspirated foreign material. It is conceivable that, as a result of the increased venosity of the fetal blood, the respiratory center may even be stimulated before birth, thus leading to aspiration of mucus, etc. More commonly, the baby's first gasp is initiated by the sudden change from the intra-uterine warmth to the cool atmospheric temperature; in breech deliveries, the head is still in the birth canal while the body has already been subjected to the stimulation of the room temperature. Whatever material may be near or within the baby's mouth, can

be aspirated into the pharynx, larynx, trachea or bronchi. Hence, obstruction of the upper respiratory passages may be due to vaginal mucus, feces, amniotic fluid, blood or meconium. This foreign material interferes with the entrance of air, and hence oxygen, into the pulmonary area to carry on proper respiration.

Prolonged and difficult labor, prolapsed cord, undue pressure upon the cord, low implantation of the placenta or its too early separation, and maternal convulsions, all act more or less in the same manner to bring about cyanosis. They cause cerebral anemia and consequent failure of the respiratory center to function. They interfere with the proper exchange of gases, leading to a disturbed carbon dioxide-oxygen relationship in the fetal blood, for cyanosis may be due either to increased carbon dioxide, or diminished oxygen, or a decreased carbon dioxide and oxygen content of the blood.

Narcotization by too large a dose of nembutal and its derivatives or by too much morphine or by morphine administered between four hours to a half hour before delivery, may interfere greatly with initiation and continuation of respiration. These sedatives apparently have too depressing an effect upon the fetal respiratory center. DeLee<sup>3</sup> says that "morphine must be given at such time that the fetus will have recovered from its effects before it is born, or at a moment when we are certain the drug will not have passed over to the child in any considerable quantity by the time that it is delivered; morphine may be given up to four hours before birth, but not from then on until thirty minutes before delivery." Dunham<sup>4</sup> found that in a group of mothers in whom there was no history of any condition other than the administration of morphine, which of itself as far as could be determined might account for delay in respiration of the infants, when compared with a similar group of mothers who had no morphine, there was a delay in respiration in 15 per cent of the infants born to the former group, whereas in the mothers who had no morphine before delivery, only 4 per cent of the infants suffered with delayed respiration.

In cerebral edema as well as hemorrhage, the respiratory center is depressed in its activity and hence there is a lack of the normal amount of carbon dioxide which is the necessary stimulus. If the hemorrhage is supratentorial, the increased intracranial pressure is more equally divided; however, in infratentorial hemorrhages, there is greater pressure on the basal structures of the brain, resulting in greater cyanosis. Hunt,<sup>5</sup> whose investigation is based upon 600 consecutive autopsies performed upon infants who died at the New York Nursery and Child's Hospital over a period of five years, selected 118 patients whose death occurred before one month of age and who showed definite cyanosis of more than a transient nature. Injury to the brain or meninges was found more frequently than either pulmonary involvement or cardiac anomalies. Occasionally, cerebral hemorrhage and atelectasis coexisted and the latter was secondarily the result of the hemorrhage. Cerebral trauma depresses the respiratory center sufficiently to interfere with proper respiration and alveolar opening. As a result of this atelectasis a secondary pneumonia may result. Hunt<sup>5</sup> in his series of 118 autopsies found only four cases of severe atelectasis, but in each instance there was also a large cerebral hemorrhage, which was probably the primary lesion. It must be borne in mind, however, that this great proportion of cases of intracranial hemorrhage as a cause of cyanosis were all fatal ones. Fortunately, the greater majority of infants suffering from neonatal cyanosis do not have an unfavorable outcome and they must therefore have a less serious pathologic condition underlying the cyanosis.

Phrenic nerve injury, if present, is usually associated with brachial palsy. If the latter condition, therefore, is associated with cyanosis, one must consider an injury to the phrenic nerve, which is made up of the fourth and fifth cervical spinal nerves, and hence a part of the brachial plexus. Injury to that nerve causes interference with diaphragmatic action and hence disturbed respiration and cyanosis.

Not all cases of congenital cardiac anomalies cause cyanosis; in fact many of them are never associated with cyanosis.

The congenital heart diseases may be divided into the cyanotic group (venous-arterial shunt) and the noncyanotic group (arterial-venous shunt). For our purposes it will suffice if we consider only the former group. Abbott<sup>6</sup> says: "The dependence of congenital cyanosis upon deficient oxygenation is now definitely established; that the circulation evidently accommodates itself to a certain degree of oxygen unsaturation, whether brought about by obstruction in the course of the pulmonary artery, by a general retardation of flow, or by a mingling of venous with arterial blood, but that as soon as deficient oxygenation reaches a certain limit, this becomes insufficient for the needs of the body and cyanosis results.

"Cyanotic Group (*Morbus coeruleus*).

"1. Cases of venous shunt (arranged in order of severity of shunt).

"(a) Moderate cyanosis. Dextroposition of aorta with defect at base of ventricular septum; complete absence of ventricular septum; pulmonary stenosis of inflammatory type with closed ventricular septum and patent foramen ovale; tricuspid atresia with interauricular septal defect and transposition of the great trunks.

"(b) Marked cyanosis. Pulmonary stenosis with dextroposition of aorta and interventricular septal defect (tetralogy of Fallot); pulmonary atresia with ventricular septal defect, dextroposition of the aorta, and patent ductus; transposition of arterial trunks with ventricular septal defect and dextroposition of the aorta.

"(c) Extreme cyanosis: Complete absence of cardiac septa (*cor biloculare*); complete defect of aortic septum (*persistent truncus*); transposition of arterial trunks with patent foramen ovale and patent ductus but closed interventricular septum; pulmonary atresia with closed ventricular septum, patent foramen ovale and patent ductus; aortic and mitral atresia with defect of interventricular septum and aplasia of aorta."

Pulmonary atelectasis has been given entirely too much prominence as an etiologic agent in cyanosis or asphyxia of the newborn, particularly in full-term infants. As a disease

entity *per se*, it is clinically found much less frequently and discovered at autopsy still more rarely. It is supposed to cause cyanosis by its interference with the entrance and exchange of gases in the alveolar spaces. According to Loewy and von Schrotter,<sup>7</sup> two thirds of one lung may be rendered useless by bronchial obstruction before cyanosis appears. Hunt,<sup>5</sup> concludes, as a result of his autopsy studies of the 118 newborn babies with cyanosis mentioned above, that "it was not possible in any instance to demonstrate sufficient pulmonary atelectasis to warrant the assumption that it was the sole cause of the cyanosis." It is now well known that a certain amount of atelectasis is present in all newborn infants, and with age, crying and breathing, the atelectasis clears. All the alveoli in the lungs are not opened up with the first gasp; it takes days or even weeks before the entire lung surface is unfolded; for this reason a certain amount of atelectasis may almost be spoken of as physiologic. In premature infants particularly there is not only a certain degree of this type of atelectasis, but there are also areas of undeveloped lung tissue which, it is presumed, in time grow into normal alveolar structures. It is probably on this account that cyanosis is so much more common and more severe in the premature.

It is now generally conceded that the rôle of an enlarged thymus gland as a cause of asphyxia and cyanosis in the newborn has been overestimated. The author,<sup>8</sup> in a study of 1074 newborn infants for enlarged thymus, found the gland to play a practically negligible, if any, rôle, in the causation of cyanosis. The cases, in which the roentgenologist reported an enlarged thymus with encroachment upon trachea, were found at autopsy to suffer with either cerebral hemorrhage or pneumonia as a cause of the symptoms.

Diaphragmatic hernia, although rare as a cause of cyanosis, will, if present, contribute to the symptom through the encroachment of the abdominal viscera upon the thoracic cavity and displace lung tissue as well as the heart.

Prematurity, as we mentioned elsewhere, is a most common cause of cyanosis. There are several reasons for this oc-



currence. In the first place, the respiratory center is only partially developed; this makes it less susceptible to carbon dioxide stimulation. The above-mentioned undeveloped lung tissue is another important factor. The premature and immature infant is much more susceptible to intracranial edema or cerebral hemorrhage thus increasing the cyanosis. Finally, sepsis, and particularly pneumonia, is more often a complication of prematurity than of full-term infants, thus enhancing the cyanotic tendency.

Hypoplasia of the mandible (micrognathy) causes cyanosis by the tendency to tongue swallowing. As a result of the short mandible, the tongue is displaced backward, and acts as a simple mechanical factor in obstructing the air flow.

Respiratory infections cause congestion of the bronchi and alveoli and interfere with the proper exchange of gases. These infections as well as other septic infections may by their fever and toxins also act upon the respiratory center in a deleterious manner.

Of late, it has been recognized that some convulsions of the newborn may be due to tetany, a metabolic disturbance. Not only may this condition be responsible for convulsive seizures, but as a result of the laryngo- or bronchospasm, less air enters the alveoli and air hunger resulting in oxygen unsaturation and cyanosis may result.

**Diagnosis of Cause of Cyanosis.**—As in every other branch of medicine, a thorough history of the case yields invaluable information to aid in the proper diagnosis. Here, the obstetrician rather than the parent is called upon to give the desired data, particularly when it is suspected that the cause of cyanosis might be an accident of labor. Was the mother in good health or did she suffer from some chronic or debilitating ailment in the last months of her pregnancy? Was labor prolonged and difficult? Was it a breech delivery? Breech births are more susceptible to cerebral hemorrhage. Was it a long and exhausting labor and were forceps applied as a last expedient? Was morphine or nembutal administered? If so, how much and how long before the delivery of the baby?

A narcotized infant can be recognized by its inactivity, drowsiness, cyanosis, the difficulty with which it is made to cry, the slow heart action, and perhaps, though rarely, pin-point pupils.

Cerebral edema and cerebral hemorrhage are sometimes very difficult to distinguish. The final diagnosis may sometimes not be made until many months have elapsed and the infant has developed into a normal baby; then one often revises the diagnosis from hemorrhage to edema. Even then one cannot be certain, because many a case of multiple punctiform hemorrhages of the brain clears without leaving any residual symptoms. In the long run, as far as therapy is concerned, it makes little difference whether a diagnosis of edema or hemorrhage of the brain has been made, because the therapeutic measures to be undertaken are more or less similar in the two conditions. An infant whose cyanosis is intermittent rather than continuous is usually suspected of suffering an intracranial injury. Intracranial hemorrhage is of the meningeal type in the large majority of the cases. If the hemorrhage is cortical, convulsions are more apt to occur than when it is basal. In infratentorial hemorrhage, the symptoms are more severe, cyanosis more profound, and breathing more labored, because of the greater pressure exerted upon the respiratory center. There may or may not be difficulty in initiating respiration. The infant may respond well soon after birth and not exhibit any signals of trouble for twenty-four to forty-eight hours or even seventy-two hours. Occasionally, though more rarely, symptoms may not set in for three to four weeks after birth. If the intracranial pressure is increased, the pulse may be slow, respirations irregular, intermittent or continuous cyanosis, the anterior fontanel is bulging, there may be rigidity of the extremities, increased reflexes, nystagmus and sometimes retinal hemorrhages are demonstrable. Any infant that cries continuously soon after birth, or is unusually somnolent, refuses to nurse, is unable to swallow or vomits—and particularly if it is of the explosive type—should be suspected of suffering from cerebral edema or hemorrhage. A very helpful diagnostic pointer of cerebral trauma which the author

has observed is the following picture: an infant who has grunting respirations similar to the expiratory grunt of pneumonia in older children, or has sighing respirations, and whose cheeks and lips pout and collapse rhythmically with each expiration, accompanied by foaming saliva at the front of the mouth or between the lips, most frequently has some intracranial birth trauma. The spinal or cisternal puncture is by no means a certain diagnostic procedure. Clear fluid has been obtained in cases that later proved to be undoubted cerebral hemorrhages; on the other hand, about 10 per cent of all newborn infants may show red blood cells in the spinal fluid, although they show no signs of cerebral hemorrhage and later develop no residual symptoms. Furthermore, the finding of a xanthochromic fluid is no sign of hemorrhage, because icterus may give the same discoloration, although it must be admitted that a positive benzidine reaction for blood on a xanthochromic fluid should make one suspicious of hemorrhage. Also the finding of crenated red blood cells in the spinal fluid may point to hemorrhage rather than to blood resulting from trauma of the plexus of veins in the spinal canal. In a word, when a spinal puncture is undertaken, one must evaluate the findings very carefully and with an unbiased mind and correlate them with the clinical findings and history of the individual case.

Phrenic nerve injury is diagnosed by the presence of an associated brachial palsy, lagging in the expansion of the lower half of the chest on the affected side and a demonstration by the fluoroscope that the diaphragm is not contracting on the affected side. Diaphragmatic hernia is usually found on the left side. Bizarre and changing physical findings in the chest make one suspicious of the condition. The finding of dulness in the thorax, to be replaced by tympany at the next examination, is a warning of its presence. The heart may be displaced to one side, usually to the right. The upper abdomen may appear collapsed, because the viscera are in the thoracic cavity. A simple x-ray film of the chest may confirm the diagnosis, although sometimes it becomes necessary to administer barium to the infant before the roentgenologic examination is made.

Pulmonary atelectasis is difficult to diagnose clinically unless it is very extensive, in which case areas of impaired resonance are found with absent breath sounds. The cyanosis in those cases is usually of the continuous type. If a whole lobe or the greater part of it is collapsed, one usually finds the heart drawn over to the affected side. The x-ray examination of the lungs makes the final diagnosis certain. If pneumonia has developed, there are in addition to the continuous cyanosis, a septic temperature, rapid respiratory rate, cough, and auscultatory signs of pneumonic consolidation. Pneumonia of the newborn is much more common than is generally believed, and it is usually an aspiration pneumonia. Farber and Sweet<sup>9</sup> demonstrated amniotic sac contents in the lungs of 88 per cent of 124 infants who died shortly after birth and they pointed out the importance of such aspiration as a cause of respiratory embarrassment in the newborn.

Enlargement of the thymus gland as a cause of cyanosis in the newborn, is much more rare than the frequency with which such diagnosis is made. Besides the cyanosis, there may be dyspnea, crowing sounds, such as result from laryngeal compression, and choking, particularly during feeding. Clinical demonstration by percussion of the enlarged thymus gland is only certain if the gland is very much hypertrophied. An x-ray study must be made of the infant's chest and neck in both views, anteroposterior as well as lateral. Only then should one be satisfied with the diagnosis of hypertrophied thymus gland, if all other common causes for cyanosis have been excluded, and if in addition to the clinical signs there is unmistakable roentgenologic evidence of hypertrophy associated with encroachment upon the trachea.

The diagnosis of a congenital heart defect as a cause of the cyanosis is easy, if one finds cardiac enlargement, a thrill and a definite murmur or murmurs. Sometimes only one or two of the above signs suffice for the diagnosis. One must bear in mind, however, that congenital heart disease may exist without any clinical signs. In some cases a murmur is not heard at birth, but becomes evident several days or weeks

later. In other cases, a murmur discovered soon after delivery later disappears altogether or changes in time and quality. Sometimes the x-ray examination of the heart may aid in the diagnosis of congenital heart disease, but more often—on account of the normally found globular-shaped heart in many infants at birth—the cardiac shadow as delineated by the x-ray only adds confusion to the problem. In any event, one is not very much amiss in failing to diagnose a congenital cardiac defect, because therapeutically there is practically nothing that one can do to relieve the condition.

Tetany is a disease entity that has been recognized of late as occurring in the newborn. Formerly it was believed that tetany is a disturbance that only affected infants after the third month of life. In the past few years, however, there has been an increasing number of cases of tetany in the newborn reported in the literature. Besides cyanosis, the symptoms that may be observed are laryngospasm, convulsions, carpopedal spasm or, in its absence, a positive Trousseau sign and a positive Chvostek (facialis) phenomenon. Increased excitability to the faradic current (Erb sign) and a decreased blood calcium with a high blood phosphorus content make the diagnosis certain.

**Treatment of the Various Causes of Cyanosis.**—Whatever methods or measures are employed in the relief of the particular cause of the cyanosis, three general principles are to be observed and practiced in all cases, namely: (1) be gentle; (2) maintain the body heat; (3) clear the air passages before any attempt at respiration is made. We need not emphasize here how labile the newborn, and particularly the premature infant is; how easily bones may be broken or dislocated if too vigorous attempts are made to initiate respiration; how frequently small hemorrhages in the brain may become more extensive if the, forever to be forgotten, Schultze swinging method of resuscitation is practiced. Whether artificial respiration by rhythmic contraction of the thorax is practiced, or whether the lower half of the body is rhythmically compressed against the chest, or whether mouth-to-mouth insuffla-

tion is practiced, one must be gentle and unhurried in carrying out the procedures, or harm will result. In the last-mentioned method, gentleness is paramount, otherwise rupture of the alveoli may follow. The sudden change from the warm intra-uterine surroundings to the cool room temperature, while it is considered by some as beneficial in that it helps to stimulate respiration, nevertheless, if continued too long will lead to excessive heat loss, shock, loss of weight and other unpleasant complications. Immediately after the baby is born, it should be wrapped in warm blankets and kept in a heated bassinet or incubator, where all the necessary toilet of the eyes, cord and skin should take place. Clearing the air passages of foreign débris before any attempt at respiration is made will obviate much trouble and cyanosis later. In fact, the best time to first aspirate is when the head has been delivered, but before the remainder of the body has been extracted; otherwise the sudden change from the warm intra-uterine cavity to the cold air may initiate the first gasp, and material will be inhaled causing not only cyanosis and asphyxia, but also pneumonia. Usually the compression of the chest that accompanies perineal deliveries expresses most but not all of the débris and mucus from the respiratory tract. However, in cesarean sections and also to some extent in breech deliveries, thoracic compression does not take place and hence more thorough aspiration of mucus must be instituted.

Aspiration is usually performed by means of a small cannula attached to a piece of rubber tubing. A glass bulb to catch the aspirated material is inserted between the cannula and rubber tubing. Suction is practiced by mouth. With this method most of the foreign material present in the mouth and pharynx can be removed. In many infants cyanosis recurs after they are brought into the nursery and in them the cyanosis may be due to thick mucus or blood in the rhino- or laryngopharynx. The author has found the following method very helpful in removing the foreign material from those parts: a number 8 or 10 French catheter is attached to an ordinary nose and throat suction apparatus, preferably one whose suc-

tion power can be regulated. The catheter can be introduced into the nose, laryngopharynx and occasionally even upper laryngeal aperture; gentle suction is applied. It is amazing how much mucus and débris can be removed thus, which the ordinary cannula could not reach. Furthermore, the cannula is likely to traumatize the mucosa of the mouth and pharynx, whereas the soft thin rubber catheter is quite harmless.

After the foreign material has all been cleared away from the respiratory pathway, the next most important step in the treatment of the cyanosis is the administration of either a mixture of 5 per cent carbon dioxide and 95 per cent oxygen or pure oxygen alone. There is some controversy as to which of the two is more indicated. Henderson<sup>10</sup> says: "After birth the infant breathes in response to the same stimulus and by the same mechanism as those which the modern physiology of respiration has shown obtained in adults, in children, and in all mammalian animals. In all these, and in the infant no less, the maintenance and regulation of breathing depend on the carbon dioxide brought to the respiratory center in the blood. Oxygen is requisite if the center itself is to be maintained in normal condition, and if the tissues are to produce carbon dioxide, for deprivation of oxygen necessarily decreases the production of carbon dioxide. But the center may be quite normal and also quite inactive in the presence of ample oxygen if the blood is deficient in carbon dioxide. If the center has become inactive, or if its activity is subnormal, there is one, and only one, stimulus that will both restore and maintain normal activity; an increase of carbon dioxide in the blood. . . . It is as certain as anything in the whole range of modern science that respiration is under a chemical control by the more or less direct action of the arterial blood, chiefly through its content of carbon dioxide, on the respiratory center in the brain. It has been proved also that oxygen is not a stimulant, a fact which clinicians seem to find extremely hard to appreciate. . . . Asphyxia is usually thought of as a condition of oxygen deficiency and excess of carbon dioxide. This is a misconception; asphyxia usually, as in the typical condition of carbon monoxide

poisoning, involves both low oxygen and low carbon dioxide content in the blood and tissues. . . . It is the carbon dioxide carried by the blood from the tissues to the brain that is the physiologic stimulant to respiration. When the center is depressed it requires more than the normal amount of this stimulant to induce activity." On the other hand, Kane and Kreiselman<sup>11</sup> who studied the carbon dioxide content of the cord blood in 7 asphyxiated, 26 gasping and 14 crying infants, found that the carbon dioxide content in the newborn is consistently high and that the proportion of carbon dioxide increases with the degree of asphyxia. (In the 7 asphyxiated infants, the carbon dioxide averaged 54.6 volumes per cent.) They reasoned therefore that the addition of carbon dioxide to oxygen as a resuscitating agent is contraindicated; in fact, they found that the instillation of pure oxygen into the lungs was sufficient to initiate respiration in the newborn. Similarly, Eastman<sup>12</sup> who made some very valuable studies on fetal blood, concluded that the use of carbon dioxide as a resuscitating agent in asphyxia neonatorum is not only superfluous, but may even be harmful, in that it tends to aggravate an already existing acidosis. He, therefore, advocates the employment of oxygen alone as the therapeutic agent for the treatment of cyanosis or the graver condition, asphyxia neonatorum. Whether one employs oxygen alone or oxygen in combination with carbon dioxide, it is a most useful and certain adjunct in the therapeusis of cyanosis. It may be administered through a mask applied over the face of the infant or by means of a number 8 or 10 French rubber catheter inserted into the nostril of the infant, so that the tip can just be visible in the mouth at the level of the soft palate. The administration is at first continuous and, depending upon the severity of the individual case, intermittently for twelve to twenty-four to forty-eight hours or even longer if necessary.

Where other methods of aiding respiration had been tried without beneficial effect, the infant respirator has been used successfully. The principle of the Drinker respirator consists in placing the infant in a metal box, fairly airtight, with



the head protruding. One electric motor institutes negative pressure, thus inducing inspiration as a result of air entering the lungs through the nose and mouth. As atmospheric pressure is restored within the respirator, expiration occurs as a result of the elastic recoil of the chest. This, as well as a modified form of the Drinker respirator, has been used successfully, not only in full-term, but also in premature and immature cyanotic and asphyxiated infants. In the absence of a tank of carbon dioxide and oxygen or of oxygen alone, mouth-to-mouth insufflation is a very valuable adjunct, provided it is done gently. With a piece of sterile gauze placed over the infant's mouth, the operator gently blows his breath into the infant's mouth at the rate of about twenty to twenty-four times per minute. However, here as well as with the use of a mask over the baby's face, gentleness is the watchword, otherwise alveolar damage might result. When we remember that the exhaled air contains 16 per cent oxygen and 4.38 per cent carbon dioxide, we realize why it is a valuable substitute as a respiratory stimulant.

If the cyanosis is the result of intracranial hemorrhage, in addition to administering carbon dioxide and oxygen, the infant is kept warm, and disturbed as little as possible. If the fontanel is bulging and signs of increased intracranial pressure are evident, periodic spinal tapping is advocated until the pressure is normal, but the procedure should be carried out with a minimal amount of handling of the baby. If it is suspected—as a result of a family history of bleeder's disease or a prolonged coagulation time—that a spontaneous rather than a traumatic hemorrhage is the underlying condition, then and only then should parental blood, in amounts of 15 to 30 cc., be given intramuscularly and repeated in twenty-four hours if there is no improvement, or larger amounts of blood may be transfused intravenously. Sedative drugs—particularly phenobarbital in adequate dosage—are indicated where restlessness is a prominent symptom.

There is, of course, very little that one can undertake in the treatment of cyanosis that is caused by a congenital cardiac

defect, except perhaps to relieve the symptoms by the administration of oft-mentioned physiologic stimulant. Where an enlarged thymus has been definitely diagnosed as the cause of cyanosis, an immediate x-ray treatment will usually give prompt relief; occasionally, however, the thymic symptoms are temporarily aggravated immediately following the exposure to the x-ray. In infectious states, particularly pneumonia, besides carbon dioxide and oxygen, frequent changing of the infant's position, blood transfusion and appropriate treatment of the underlying infection is the method of procedure. In the treatment of atelectasis, besides the periodic insufflation of carbon dioxide and oxygen, repeated stimulation of the infant to crying is indicated. The treatment of cyanosis due to tetany consists in administering parathormone and calcium—preferably the gluconate—intramuscularly, later continuing the calcium orally for some time and either keeping the infant on breast milk or placing it on an acidified milk formula. In hypoplasia of the mandible, Eley and Farber,<sup>13</sup> who reported 5 cases, recommended postural treatment, *i. e.*, placing the infant on the face and elevating the remainder of the body. This usually relieves the mild cases; if the micrognathia is severe, a simple brace to hold the mandible forward and at the same time exerting pressure against the floor of the mouth and base of tongue has been used with success. Cyanosis or asphyxia resulting from overnarcotization is best treated by the application of external heat, oxygen, alpha-lobeline  $\frac{1}{40}$  to  $\frac{1}{20}$  grain intramuscularly or intravenously, artificial respiratory efforts and finally the Drinker respirator. In employing alpha-lobeline, one must remember that its action as a respiratory stimulant is very fleeting and may therefore be repeated at fifteen- to thirty-minute intervals if necessary.

Vigorous spanking, slapping the infant, dipping it alternately in warm and cold water, thus chilling and shocking the infant, blowing cigarette smoke into the baby's mouth, rhythmic traction of the tongue, dilation of the sphincter ani, pouring ether on the baby, and many other similar measures that are in vogue in one clinic or another, are all crude and primi-

tive; some are unphysiologic, and most of them are productive of more harm than good.

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### TREATMENT OF CHRONIC ENDOCERVICITIS AND VULVOVAGINITIS

#### TREATMENT OF CHRONIC ENDOCERVITIS

CHRONIC endocervicitis is probably the most common and, at times, the most difficult gynecological condition to treat. This is readily explained when the histologic anatomy of the cervix is studied.

The cervical canal is  $1\frac{1}{4}$  inches in length, measured from the external to the internal os. The wall of the canal presents an anterior and posterior longitudinal ridge, from each of which proceed a number of small oblique columns, the palmate folds, giving the appearance of branches from the stem of a tree. To this arrangement the name "arbor vitae" is applied.

In the upper two thirds, the canal is lined with columnar, ciliated epithelium and is provided with racemose glands which secrete a clear, viscid, alkaline mucus. In the lower one third the mucous membrane presents numerous papillae and there is a gradual transition in the epithelium to stratified squamous close to the external orifice. On the vaginal surface of the cervix the epithelium is stratified squamous. It is not uncommon for the columnar epithelium to be continued a little outside the external os, appearing as a well-defined bright red area, circular or possibly irregular in outline. The racemose glands have narrow, tortuous ducts and provide an ideal location for bacterial growth. The inaccessibility of these glands within the folds of mucosa makes it quite difficult to reach them with ordinary chemicals.

Infections and traumatic lesions of the cervix will very

often cause an alteration in the usual relationship between the columnar and squamous epithelium. This again is manifested by a bright red color when the cervix is exposed with a speculum.

The following conditions may give rise to this typical appearance: (1) "pseudo-erosion"—a congenital extension of the mucosa of the cervical canal beyond the external os; (2) "ectropion"—an acquired extension of the mucosa of the cervical canal beyond the external os, caused by infection of the mucosa; (3) "eversion of the cervical lips"—causing exposure of the cervical mucosa. This may be a congenital split or resulting from a laceration during labor or abortion; and (4) "true erosion" of the cervical mucosa with primary loss of surface epithelium brought about by infection or trauma (mechanical, chemical, or thermal). Any combination of the above-mentioned conditions may exist and the appearance may be further distorted by the development of nabothian cysts which result from the blocking of the ducts of the cervical glands.

The object of treatment is to destroy infection within the cervical canal or upon the vaginal surface of the cervix, to correct everted lips, to obliterate distended glands, or to remove hypertrophied cervical lips. Cervical and urethral smears should precede any form of treatment.

To destroy infection, treatment should endeavor to localize active infection and promote drainage. When the cervix is hypertrophied and contains cysts, hot douches and puncture of the follicle with a cautery will help. If drainage is poor the os should be gently dilated, especially in the nulliparae. Topical applications of various antiseptics may be tried after first removing the mucous plug with a solution of sodium hydroxide (10 per cent). For this purpose silver nitrate solution (20 to 50 per cent), mercurochrome (20 per cent), or tincture of iodine are serviceable. Tampons covered with petrolatum should be inserted in the vagina following these applications and removed in six to eight hours. The patient is then instructed to take a daily douche and the topical ap-

plication repeated in one or two weeks. When the cervical condition is improved operative or cautery treatment may be instituted.

In the gynecologic department at Jefferson Hospital the cautery is the method of choice in treating chronic endocervicitis. It is well to remember the necessity for preserving the cervix for future pregnancies if the patient is in the child-bearing period. It is also important to have the cervix clean and to be certain that there is no active infection present. When eversion alone exists, cauterization of the everted lips will suffice to correct the condition. In the nulliparae when the os is constricted it is desirable to split the cervical lips, expose the entire mucosa of the canal, and then cauterize the involved area. Following this procedure a stitch is placed at the summit of the cervical incision. This prevents an adherence of the cervical lips. In virgins and women of child-bearing age, cauterization should be limited to a depth of 5 mm. In multiparae the cervical os is usually open and the canal accessible.

The contraindications to cauterization are acute cervical infections and the existence of an acute or subacute salpingitis. Pregnancy is not necessarily a contraindication to the use of the cautery. Breckenbridge and Whitehouse have shown that this method is safe and advisable in treating chronic gonorrheal endocervicitis in pregnancy. However, it is well to remember that the injudicious use of the cautery during pregnancy may cause abortion.

The complications that may result from cauterization are: (1) vaginal burns, (2) hemorrhage, and (3) stenosis. Burns are best prevented by thoroughly drying the vagina and cervix when an alcoholic solution is used for cleansing, and by protecting the mucosa of the vagina with retractors and moist gauze. Hemorrhage may occur immediately or seven to ten days afterward as the result of sloughing. This is best treated by keeping the patient quiet in bed or by gently packing the vagina. Stenosis can be prevented by dilatation when necessary.

After cauterization the patient is advised to avoid tub baths and not to douche unless the discharge is very annoying. If such is the case a solution of potassium permanganate (1:5000) used as a douche is permissible after the tenth day.

Persistent cervical infection is most frequently gonorrheal in origin. It is important that any foci in Skene's tubules, Bartholin's glands, and the urethra be destroyed and the patient cautioned against reinfection.

Other plans of treatment are advocated which in some instances are helpful. The use of the Elliott apparatus for producing pelvic heat is beneficial particularly when there is adnexal involvement. Desjardins, Stubler and Popp have reported good results in using fever therapy in treating gonorrhea. Hyams and Crossan report success with the radio knife. Their technic is to core out the mucous lining of the canal without destroying the musculature. Ende and Cherry recommend coagulation of the infected mucosa to a depth of 3 to 5 mm. Tovey employs copper ionization.

Operative procedures to correct hypertrophy of the cervical lips may be necessary especially after the menopause, and should be undertaken only by those well trained in the treatment of gynecologic conditions. For complete surgical details the reader is referred to textbooks dealing with the operations of trachelorrhaphy and trachelectomy.

#### TREATMENTS OF VULVOVAGINITIS

Vulvovaginitis may occur at any period in life. In childhood the vaginal mucosa is quite susceptible to infection and this is also the case in those past the menopause. Between puberty and the menopause the vaginal epithelium is more resistant to infection but during this period it is subject to such devitalizing influences as trauma, irritating discharges from the cervix, and constitutional disturbances, factors which predispose to infection. The exciting cause is some microorganism, animal parasite or fungus. The treatment, therefore, will depend upon the age of the patient and the causative factor.

Before any form of therapy is considered smears should be made and a definite diagnosis established.

#### GONORRHEAL VULVOVAGINITIS IN CHILDREN

The treatment of gonorrheal vulvovaginitis in children is always difficult. Cleanliness is the prime essential and frequent bathing with soap and water will help to remove any discharge from the external genitalia. The child should have its own clothing, towels, etc., and must be kept from contact with other children. Douches are necessary and can be administered by the mother after proper instruction. Antiseptics that irritate the mucosa are contraindicated. Potassium permanganate (1:5000) or boric acid solution, in gallon quantities, are not irritating. The interior of the vagina may be treated through a Kelly cystoscope with the child in the knee-chest or Trendelenburg position. For this purpose silver nitrate or mercurochrome may be used.

Gonococcus vaccines may be tried but the results are questionable.

The use of estrogenic substance has given good results in some cases. Lewis suggests using 100 rat units of theelin daily, diminishing the dose as a reaction is obtained by maintaining a vigorous squamous cell proliferation. TeLinde and Brawner report success by using amniotin in oil. They state that amniotin in suppository form has proved effective in producing mature vaginal epithelium and good therapeutic effects in gonococcal vaginitis in all cases in which they tried it.

#### GONORRHEAL VULVOVAGINITIS IN ADULTS

The treatment is general and local. Rest is essential, the diet should be light, mild laxatives are indicated to keep the bowels open, and the urine should be rendered alkaline. The vulva should be cleansed frequently with "pitcher douches" of potassium permanganate (1:5000) or bichloride of mercury (1:4000). After these irrigations bathing the parts with castile soap and warm water and then drying with cotton is a good procedure. Hot applications of lead water and laudanum,



witch hazel, or boric acid solution will relieve vulvular itching and burning. When the acute symptoms subside the vulva and vagina may be painted with silver nitrate (5 to 10 per cent) or mercurochrome (5 per cent). Douches of Lugol's solution or "A. B. C." powder (alum  $\frac{1}{2}$  ounce, boric acid 3 ounces, phenol  $\frac{1}{2}$  ounce, oil of peppermint 5 minims) using a teaspoonful to 2 quarts of warm water, are cleansing and will promote healing. Curtis recommends the blowing of powders into the vagina. Foci of infection in Skene's tubules, Bartholin's glands, and the cervix should be removed.

#### SENILE VULVOVAGINITIS

Treatment should be directed toward improving the general health and removing the cause. Silver nitrate (2 to 10 per cent) applied locally to the vagina will often give good results. This is followed by the insertion of a tampon covered with cold cream. Douching with 0.5 per cent lactic acid solution will aid in restoring vaginal flora. Estrogenic substance (amniotin or theelin) is sometimes beneficial. The urine should be examined carefully and any abnormalities corrected. Strong soaps or irritating douches should be avoided.

#### YEAST VULVOVAGINITIS

Gentian violet in a 1 per cent aqueous solution is practically specific for this type of infection. After properly exposing the vagina, and drying the mucous membrane, a cotton applicator is dipped in the gentian violet solution and used to paint the entire vaginal mucosa. A dry tampon may then be inserted in the vagina to lessen the amount of solution that may escape. The patient is then instructed to use a mercuric chloride douche (1:4000) each morning. The application of gentian violet should be done two or three times weekly until the monilia have disappeared from the vaginal secretion.

Gentian violet is sometimes very irritating to the inflamed mucosa of young girls and elderly women. In these cases 5 per cent mercurochrome solution or 1:5000 metaphen solution may be tried.

## TRICHOMONAS VAGINALIS VULVOVAGINITIS

There are many forms of treatment, none being specific, which will result in a cure if used frequently over a period of time. The first requisite is thorough cleansing of the vaginal mucosa with tincture of green soap, and secondly applying an antiseptic to destroy the parasite. For this purpose 5 per cent mercurochrome, 1 per cent methylene blue solution, or 5 to 10 per cent silver nitrate solution are serviceable. This should be done frequently and the patient advised to use daily douches of lactic acid solution (1 teaspoonful to 1 quart of water). The use of 1 per cent picric acid suppositories as recommended by Goodall are helpful. Foci of infection should be searched for and eliminated. Probably the most important item in treating this condition is persistence.

## OTHER FORMS OF VULVOVAGINITIS

**Actinomycotic vulvovaginitis** is treated by surgical excision of the granules and the administration of iodides in large doses internally.

**Anginal Vulvovaginitis.**—Application of potassium permanganate in the proper strength for swabbing or douching and a paste of neoarsphenamine are used to good advantage.

**Diphtheritic Vulvovaginitis.**—Here appropriate doses of diphtheria antitoxin must be given supplemented by local irrigations with a mild antiseptic solution.

**Nonspecific Vulvovaginitis.**—In the treatment of this form cleanliness is of prime importance. Douches and instillations of antiseptic solutions are indicated and any general local cause must be removed.

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### NOTES IN THE FIELD OF GERIATRICS

DISEASE in old age differs in many ways from disease in other periods of life; the incidence of the various disease processes is not the same as in childhood or in middle age; the symptoms of a disease in the aged may vary considerably from the so-called "classical picture" of that disease. Similarly, the prognosis is not the same, and our treatment of disease in the old must usually be modified from our usual procedure and the inevitably limited goal of treatment in the aged must always be kept in mind.

These differences, inherent to the aging organism, are the basis upon which the science of geriatrics rests in exactly the same manner as pediatrics is concerned with the peculiarities and potentialities of the growing child.

Geriatrics is concerned with the prolongation of life, with the maintenance of physical and mental health, the relief of suffering, the lessening of the handicaps of age and the diagnosis and treatment of such diseases as occur. These are worthy aims and one need not apologize for an interest in geriatrics. Obviously it lacks some of the appeal of pediatrics for it deals with the body in involution, not in evolution. Yet it is an important subject with an increasing field of usefulness as more and more of the population are surviving past middle age. One might facetiously claim that of the two it is geriatrics which is the growing science while the falling birth rate suggests that pediatrics is a dying specialty.

## CHANGES OF SENESCENCE

It is often said that old age is itself a disease but this is not true and one must distinguish between normal physiologic old age which is called senescence and abnormal pathologic old age which is by some termed "senility." The drawing of a line between the two is not easy for the physiologic changes tend to resemble and merge into the pathologic processes common in the aged. The distinction is, however, of the utmost importance.

In order to draw this distinction we must first become familiar with the physiologic changes appropriate to the age of our patient, just as the pediatrician does. These form a sort of base line; we accept them as our patient's normal even though the findings be very much altered from those in the younger subject. In the diagnosis of disease in the old we must often ignore physiologic changes which might have great diagnostic significance if present in a middle-aged patient. And we must always remember that in the treatment of disease in the aged we must keep constantly in mind the so-called "normal state" of our patient and we must admit that our therapeutic goal is limited to the cure of the existing disease and to the restoration of our patient to a state proper to his years. To this point we will have to return later.

There is little need to mention graying of the hair except to say that it often occurs in quite young persons, especially in certain families with coarse black hair. As long ago as 1638, Francis Bacon wrote "Hasty gray hairs, without baldness, is a token of long time: contrarily if they be accompanied with baldness."

Similarly the well-known arcus senilis may occur even before middle age. Often this lipoid deposit may encircle the whole iris but it can never be employed as an evidence of great age nor of disease. It is an interesting fact that Nascher, the author of one of the most famous works on geriatrics, had an arcus senilis even as a young man; one cannot help wondering whether it was this precocious arcus which directed his life interest to the changes and diseases of old age.

The skeleton, on the other hand, shows increasing changes which are characteristic of advancing years. One of the most important is an atrophic thinning of the intervertebral disks which accounts for much of the bowing of the spine, also flattening of the vertebrae and a tendency to exostoses (Hrdlicka). The vertebral column becomes curved and shorter resulting in a loss of an inch or two in height. This forward bowing of the spine changes the shape and size of the thoracic cage and contributes in this way to the development of so-called "senile" or postural emphysema. The long bones and the larger flat bones become weakened from osteoporosis and approach the picture of Paget's disease. Many of the cartilages atrophy and become calcified.

All lymphoid tissue throughout the body atrophies as age advances. The tonsils exhibit this change even before the age of forty; the lymph nodes are markedly atrophied in the old. As a rule the thymus has almost disappeared—but it may sometimes be preserved. No effect of this lymph tissue atrophy can, however, be recognized in the number of lymphocytes in the circulating blood.

Almost all the organs atrophy and in the case of those whose function can be measured some reduction in functional ability is the rule. In those over seventy years of age the kidneys constantly exhibit atrophy and the usual tests of renal function reveal some impairment in almost 90 per cent of cases.<sup>1</sup> It is the phenolsulphonephthalein elimination test which most often gives abnormal results.

The thyroid is atrophied and the basal metabolic rate is usually lowered. The acid glands of the stomach are less evident and an anacidity is present in fully two thirds of the very old. The spleen, adrenals and liver become smaller especially the liver which may be reduced to half its normal adult weight. We have no satisfactory evidence that any of various functions of the liver are definitely impaired although it is true that in the aged the sugar tolerance test very often reveals a curve suggesting a marked storage defect.

The lungs constantly reveal emphysema and this state

must be accepted as physiologic in the aged. Whether it results from the postural changes due to spinal curvature, or from simple atrophy of elastic tissue, it is apparently very different from the obstructive emphysema of youth and middle age. With the progress of emphysema and the weakening of the muscles of respiration the vital capacity decreases. On the average there is a loss of about 600 cc. as one ages from sixty to ninety years; males losing more in proportion to their higher initial level.<sup>2</sup>

The heart is an exception to the general tendency to atrophy—its weight may maintain its relation to body weight unchanged. In the old the pulse rate tends to settle to about 60 per minute; the blood pressure often rises until the age of seventy but then lowers or remains stationary.

It is true that changes do occur in the aorta and larger arteries with great frequency but these changes are of a special kind and must not be confused with true arteriosclerosis which is always pathologic. The arterial changes of senescence affect the media of the vessel wall—first as a degeneration and finally as a calcification. The result bears the name of Mönckeberg's sclerosis and although it greatly alters the artery to palpation giving it the so-called "bird's trachea" feel, the process causes little or no impairment of circulation; nor do the lengthening of the aorta or the calcified plaques so commonly revealed in the aortic arch by x-ray of the aged subject. Some capillary beds are greatly lessened in the old—especially perhaps in the skin giving rise to the deceptive "patriarchal pallor" which so often leads us into a mistaken diagnosis of anemia. By and large, the circulation of the very old is amazingly good; their electrocardiographs exhibit no constant abnormality and their tendency to heart disease is not great.

I hope by this time I have made it clear that one must know the normal of the aged in order to recognize the pathologic when it occurs and to diagnose disease. Let me drive home my point by reference to one more organ or system.

The brain in the old becomes smaller and increasingly firm; the meninges are often adherent and areas of calcification are

common. The functional changes are only too well known—merging from mere forgetfulness as one reaches one's anecdote into the definitely pathologic states of senile dementia. More important for neurologic diagnosis perhaps are some of the changes which normally take place in the reflexes and sensation of the aging person and which may readily lead us into error.

For example, the tendon jerks lessen and even disappear—the achilles reflex being the first to be lost; only late is the knee jerk ever absent. The abdominal reflex tends to be lost rather early in senescence—but the plantar reflex persists. Loss of vibratory sensation especially in the lower extremities commences even as early as fifty and is often markedly impaired by the middle sixties. Sense of position is also impaired and there may be some diminution in perception of touch and pain. These findings could easily be used to bolster up a faulty diagnosis. The pupil of the old is small unless cataract is present and recognition of contraction to light may be difficult. The senile tremor of the aged has a rate of about 100 per minute and is not by any means to be confused with true parkinsonism.

Finally, it is worthy of note that some loss of weight seems normal for the aged. At least 5 to 10 pounds is apt to be lost after the age of sixty without there being any recognizable pathologic cause. One cannot help wondering whether this change and perhaps some of the others already enumerated may not be beneficial to the aging organism. It would be easy to argue that the loss of weight, the lower metabolism, the slower and less violent muscular movements, the diminution of sex function all tend to lessen the demands made upon the heart and circulation. It is enough for our thesis today, however, if we accept these changes as physiologic and distinguish them from the truly pathologic processes which occur.

#### DISEASES OF OLD AGE

An attempt has often been made to divide the diseases seen in old age into two groups, one containing those ailments which



occur as a rule only in the aged; the other those found in younger age groups as well. Such a division is of necessity somewhat arbitrary and inaccurate.

The famous French neurologist Charcot named as the characteristic diseases of age—senile marasmus, senile osteomalacia, atrophy of the brain, and circulatory weakness from heart weakness and arteriosclerosis. You will see that these changes include several which we have classed as physiologic.

Lewellys F. Barker includes Paget's deforming osteitis, osteoporosis, malum coxae senilis, senile anorrhexia, diverticula of the esophagus and intestine, coproliths, bronchial catarrh, emphysema, prostatic hypertrophy, cerebral atherosclerosis, senile dementia, paralysis agitans (nonencephalitic) and hyperkeratoses. Again we find listed as diseases some changes which I have preferred to put among the physiologic changes of senescence.

**Diseases of the Digestive Tract.**—We have already noted that the aged are apt to lose weight, to have little appetite and to lack gastric secretion of acid—all of these without organic disease. This must not, however, lead us to overlook the frequent instances in which the aged do develop lesions of the digestive tract.

In the esophagus of the old, pressure diverticula are quite common; these are the pressure type and result from an actual herniation of the mucous membrane through the weakened muscular coats. They are apt to occur at one of two points, either where the esophagus is narrowed as it is crossed by the left bronchus or higher where the esophagus and pharynx join. Difficulty in swallowing may be a symptom and one must not confuse this with the more or less physiologic slowing of the act of deglutition which can be demonstrated by x-ray in the aged. Cases of diverticula are not rare from the age of seventy on.

The stomach is a frequent seat of carcinoma in the aged and like many diseases at this time of life the process may be amazingly latent. There may be few symptoms and these few

are apt to be explained away as due to the patient's age. Vomiting may not occur and pain is often wholly absent.

Ulcer of the stomach, on the other hand, is increasingly rare as age increases but a case reported by Cheney and Garland<sup>3</sup> exhibited a definite ulcer of the posterior wall of the stomach in a patient ninety-six years of age; there was no sign of malignancy.

Acute appendicitis used to be thought to be rare in the old but a number of excellent reports<sup>4, 5</sup> force us to admit its fairly common occurrence in the seventies and even occasionally in the eighties. The picture differs in certain important features from acute appendicitis of earlier age periods. The onset is usually less acute; there is less pain, less fever, less vomiting. Fever may be absent, the pulse not over 100, the leukocyte count not over 15,000. As a rule the diagnosis is delayed under the belief that one is dealing with some form of partial intestinal obstruction. This diagnostic error seems to be difficult to avoid. When peritonitis develops the pus is apt to be scanty and greasy. Correct diagnosis is important; for the treatment even in the very old is surgery which is remarkably successful.

True intestinal obstruction also occurs frequently in the aged, from various causes. It is predisposed to by the lessening power of the intestinal musculature. Occasionally the obstruction is found to be due to a gallstone which has silently ulcerated its way from the gallbladder into the bowel. Dr. Ravdin operated upon such a case for us at the University Hospital a few years ago. The stone could be felt through the seventy-four-year-old woman's emaciated abdominal wall. Coproliths also may lead to obstruction, and in lesser degree fecal accumulation in the lower bowel may increase the habitual constipation of the elderly and occasionally give rise to periods of irritative diarrhea. In passing it is worthy of note that the first mention of the use of mineral oil for constipation was by John Floyer in 1724 in a work entitled "The Gallenic Art of Preserving Old Men's Healths."

Diverticulitis of the descending colon occurs in the old—

predisposed to by the long-standing constipation. The picture which results may be imagined from the name given to the condition—"the left-sided appendicitis of the elderly." A serious mistake can easily be made for the mass of thickened bowel, diverticula and plastic peritonitis may resemble even at operation a malignant process and perhaps be thought to be inoperable.

In the biliary system of the aged one finds hepatic cirrhosis not infrequently in the seventh decade of life and at all advanced ages gallstones are common. Fortunately, for the patient, colic is rare and the stone may pass down the duct or ulcerate into the bowel with little or no pain. Turner<sup>6</sup> operated upon a man of eighty-one for obstruction of the bowel. The obstruction was found in the transverse colon and was due to what is claimed to be the largest gallstone on record—weight 5 ounces, length 3 inches, width  $2\frac{1}{4}$  inches. The patient recovered. After this story we must go on to another system.

**Diseases of the Genito-urinary System.**—In this field there are two topics of main interest—kidney failure and prostatic hypertrophy and these two are often associated. With regard to kidney disease in old age we have already noted that tests of kidney function, especially the 'phthalein elimination test frequently shows some impairment without any indication of serious or progressive renal pathology. We may now add that true nephritis is not a common disease after seventy. Those individuals who have suffered progressive glomerular nephritis in middle age have usually dropped out of the race before this age is reached. Acute glomerular nephritis is rare and both acute and chronic nephrosis very infrequent.

On the other hand, some degree of nephrosclerosis or arteriosclerosis of the kidney is a very common finding at autopsy in the elderly. It is seldom the cause of death and the full picture of kidney failure from this cause is not common. Probably the situation is analogous to that regarding other arteries of the body; unless the arteries are good the individual does not survive into old age. For statistical purposes it is difficult

to draw the line between the arterial changes almost physiologic for old age and those of minor pathologic degree.

Kidney impairment from back pressure due to obstruction by an hypertrophied prostate is far more frequent than true nephritis or serious nephrosclerosis.

From whatever cause it arises a slight degree of nitrogen retention is frequent in the elderly but high azotemia and the classic picture of uremia are uncommon. Also true renal edema rarely if ever occurs in the aged. Usually there is a big cardiac element present and the cardiac failure overshadows the renal failure. Often the picture is confused—but seldom is the clinical picture or the underlying process that of a true chronic nephritis.<sup>7</sup>

Prostatic hypertrophy is so common as we pass the sixties into the seventies that one could readily include it in the list of changes physiologic to senescence. But certainly one progresses by imperceptible gradations from a symptomless enlargement into the full-blown picture of obstructive “prostatism” with renal damage, raised blood pressure and nitrogen retention. We need only remind ourselves of the rarity of true nephritis in the elderly male and the frequency of what may be called an obstructive nephropathy to make the resolution never to make the former diagnosis until we have excluded the latter. Digital examination by rectum is not sufficient for a median bar may cause great obstruction even without much general enlargement of the prostatic gland. Nor should we neglect the possibility of prostatic obstruction even in the very old—for it may first cause trouble in the eighties and may be operated upon successfully even in the nineties.

**Diseases of the Lungs.**—We have mentioned the emphysema and loss of vital capacity which always occur in age and sometimes the emphysema becomes of such grade as to deserve to be termed pathological. The other diseases of the lungs which deserve to be mentioned are chronic bronchitis, tuberculosis and pneumonia.

Chronic bronchitis often termed “senile catarrh” is an extremely frequent malady of the old—so much so that few es-

cape the annoyance of the resulting cough, expectoration and dyspnea. At times the fibrosis and dilatations of the bronchioles lead to bronchiectasis and in many instances some degree of congestion from weakening circulation further interferes with respiratory function. Cyanosis from these combined factors is a common symptom in the elderly.

Tuberculosis of the lungs at advanced ages is not as rare as one might anticipate. Many authors have emphasized this and the great Laënnec recorded the finding of pulmonary tuberculosis at the autopsy of an almost one-hundred-year-old individual. Some have even claimed that more old than young persons die from tuberculosis, but this is by no means an accepted fact. Much of the evidence is old and possibly open to question. Schlesinger<sup>8</sup> in his extensive work on Diseases of Old Age emphasizes the importance of nutritional disorders, diabetes, influenza and trauma as favoring the breaking out of a latent or almost healed chronic lesion.

The *x*-rây evidence of pulmonary tuberculosis in the elderly is said to be simulated by the lung changes characteristic of old age so that this modern method of diagnosis may also lead us into error.<sup>9</sup> On the other hand, syphilis seldom causes disease or death in the very old; some of its residua may be present in the aged, but its symptoms rarely appear first at that age.

Pneumonia usually of the lobular or bronchopneumonic form is very common in the old and is frequently fatal. True croupous lobar pneumonia does occur even at advanced age but bronchopneumonia is at least five times as common. The clinical picture in the aged may differ sharply from that in a robust individual of middle age. Indeed the symptoms may be so few that an octogenarian may seem to die of myocardial failure and the discovery of an extensive pneumonia at autopsy comes as a distinct shock. Cough, fever and expectoration may all be absent and there may be little or no leukocytosis and no pleuritic pain. Also the emphysema may help hide the consolidation on physical examination and one may attribute the râles to bronchitis and passive congestion.

Possibly some of the lack of symptoms of infection may

be explained if it is true that many instances of senile pneumonia commence with a local thrombosis rather than with a true pneumococcus infection.

Pneumonia has been called by Osler "the old man's friend" because it offers a short and often peaceful final step—but by no means are all cases of pneumonia fatal even in the very old. Parkes-Weber,<sup>10</sup> the well-known British clinician, has recently reported recovery from acute pleuropneumonia at eighty-five and refers to recovery in a patient of one hundred and three who, however, developed a fatal gangrene of the foot during convalescence.

Certain of the characteristics of acute infections in the aged need to be mentioned.

**Acute Infections.**—It is generally said that except for pneumonia, influenza and erysipelas, acute infections are rare in the aged. This is statistically true—but other infections do occur and because unexpected are often overlooked or misdiagnosed. Even the so-called "childhood diseases" may occur late in life. Rolleston<sup>11</sup> has reported chickenpox at sixty-four and at seventy-six although Van Genser found no patient over sixty-five among almost 30,000 cases. Measles at seventy-one with recovery has been recorded.<sup>12</sup> And so on with other diseases.

There is one disease common to youth which shows no mercy to the aged. This is whooping cough. Many cases over seventy and not a few over eighty are on record—for example, the famous Sir William Jenner was attacked when over sixty-five years of age. Often the patient may give a history of an attack in childhood but this does not prevent the illness being severe and exhausting even to a fatal outcome. It has been emphasized<sup>13</sup> that it is not safe for the old to have contact with cases of whooping cough for any earlier immunity may have been lost and the disease is more serious to the old than to younger adults. This is worth remembering for often the grandmother is called into service to care for a child.

Pneumonia we have discussed; influenza does not differ much from the picture in earlier life; but concerning erysipelas

it is worth pointing out that its frequency in the aged reflects the poor nutrition of their skin. In the old, itching is frequent and so is eczema; keratoses and excoriations are common. Like senile pneumonia erysipelas may cause little fever and leukocytosis, but may initiate acute pyogenic infection of the kidneys of serious import.

Incidentally, it may be noted that herpes zoster in the aged is apt to leave behind it persistent local pains. Also in the aged gangrene of the skin may follow very minor injury.

Finally with regard to all acute infections in advanced age, it may be said that circulatory collapse may occur early; respiratory complications are common; delirium is frequent, but fever, leukocytosis and splenic enlargement often fail to appear.

**Diseases of the Skeleton.**—In the skeletal system the lesions of the greatest geriatric interest are Paget's disease, fractures and multiple myeloma. In Paget's disease, we are faced again with the difficulty of drawing the line between the usual osteoporosis of senescence and the process which justifies the name Paget's disease and which may be responsible for severe pain, deformity and disability. Nor must we forget that Paget's disease may appear in persons younger than the age usual for senile osteoporosis. Although it is tempting to relate Paget's disease to hyperparathyroidism, the evidence seems still to be opposed to this view.

Fractures, especially of the thinned and weakened neck of the femur, were formerly one of the tragedies of old age. To-day while no less common the much improved results of treatment make the condition much less dreaded. Healing with union has been repeated in patients over ninety<sup>14</sup> and even over one hundred.

Perhaps multiple myeloma is not common enough to be mentioned in such a hasty review as time permits today, but it is so apt to be overlooked and the pain, loss of weight and anemia blamed on something else that I cannot help reminding you that it is one of the diagnostic pitfalls in the elderly.

**Diseases of the Endocrine Glands.**—One is tempted to generalize that all endocrine functions tend to be lessened as

age advances and that distinct endocrine diseases are rare in the old. Both these statements are almost the truth. Nevertheless, it must be remembered that we are not yet sure that osteoporosis and Paget's disease of the bones are not related to disturbance of the parathyroids. Also thyrotoxicosis is commoner than one might at first think. A report<sup>15</sup> of thyroidectomies for thyrotoxicosis includes 200 cases over the age of fifty and up to the age of seventy-six.

Loss of gonadal function is more physiological than pathological—but worry about the loss may almost become a disease. Witness the absurd lengths to which efforts at its restoration have gone. No measure has ever brought about true rejuvenation; at most a temporary erotization has been achieved.

The hypophysis continues to function even in the old, and the hypophyseal sex hormone has been found in the urine of old men,<sup>16</sup> and Zondek<sup>17</sup> has found prolactin in the urine of some women up to the age of ninety-six.

**Diseases of the Cardiovascular System.**—We have already noted that in the aged it is the rule for the myocardium to be a little weakened, for the larger vessels especially the aorta to be somewhat lengthened, tortuous and perhaps calcified and for the blood pressure to be a little high. Nevertheless, it is interesting how good the circulation is apt to be in the old. A recent study of 300 individuals between eighty and one hundred years of age reported<sup>18</sup> from France supports these facts. Willius<sup>19</sup> in this country found 45 per cent of 700 persons between seventy-five and ninety-six in age had no evidence of heart disease.

Heart failure is, however, a very important disease and is one of the most frequent causes of death in the old. Often the heart fails with little previous evidence of myocardial disease and with little of the usual picture of congestive heart disease. It is perhaps a failure of nutrition of the muscle—partly from lessened blood supply, partly perhaps from lowered blood sugar or similar factors.

True congestive heart failure is not rare and is often exaggerated by the pulmonary fibrosis and emphysema. The val-



vular lesion most characteristic of advanced age is pure aortic stenosis. It is more a matter of calcification than of arteriosclerosis and the aorta beyond may be remarkably healthy as Rolleston and Christian have emphasized. Osler is quoted as saying that such narrowing of the aortic orifice "helps make a man an octogenarian."

Extensive atheroma of the aorta may occur and may indeed lead to the nonluteic dissecting type of aneurysm known as the "aneurysm of old age."

Reports in the literature include one on the greater seriousness of sinus arrhythmia in the aged than in the young,<sup>20</sup> and one stressing the rarity of thrombo-angiitis in this age period.<sup>21</sup>

Personally, I have been impressed with the importance of transient lowering of blood pressure as the factor which precipitates arterial thrombosis whether cerebral, coronary, visceral or peripheral.<sup>22</sup> I believe that many of the cerebral manifestations of the elderly result from thrombosis rather than from the hemorrhage or arterial spasm. The fact that a person's habitual blood pressure level is high does not constitute a valid objection to this theory for it is well known that the variations up and down of the blood pressure are even greater in the hypertensive than in the normal.

**Diseases of the Nervous System.**—One of the matters which needs special discussion here concerns the cerebral circulation for many of the psychoses of the aged result from poor cerebral blood supply. In fact, it is not unusual for mental confusion, delusions, transitory palsies, etc., to improve markedly and often unexpectedly when the heart action is improved.

Of course not all cerebral deterioration in the old is on a circulatory basis. True senile dementia would disprove any such view. Also there are cerebral changes which depend upon extreme pathologic arteriosclerosis and which will not respond to any treatment.

However, it should be emphasized that it is dangerous to assume too readily that mental changes are surely due to senility. This is especially true in the so-called "presenile

dementias" such as presbyophrenia, Alzheimer's disease and Pick's disease. To make such a diagnosis without careful exclusion of pernicious anemia, syphilis and frontal lobe tumor is inexcusable.

We have now touched on most of the diseases usually considered important in the field of geriatrics. We must, however, remember that our present-day success in the treatment of certain conditions formerly fatal in youth and middle age may lead to the appearance of these in greater numbers among persons of advanced years. For example, patients with pernicious anemia or severe diabetes mellitus did not often survive into advanced old age while today with liver extract and insulin it seems quite possible that they will. It is mere speculation but it is interesting to wonder whether the picture presented by such cases in old age may not be different from what we expect. How long will such replacement therapy continue to be effective? How will an aged individual withstand continued hypodermics of insulin? How will the various changes of senescence occur in an individual who is lacking in an ability to form his own antianemic factor? These are interesting questions which we cannot at this time answer. To date there seems no limit to the success of replacement treatment with thyroid substance. Means<sup>23</sup> has recorded a case of spontaneous myxedema who has for twenty years been kept in perfect control by a daily ration of thyroid substance until she has now reached the age of seventy-seven. We must be on the lookout for the thyroid needs of our numerous thyroidectomized patients as they get older.

**Characteristics of Disease in the Aged.**—Not only does geriatrics have its own list of diseases but these maladies have certain features in common. Most important is the absence of pain and of many of the expected symptoms. "The organs suffer in silence," writes Sir Humphrey Rolleston, "without any local or general disturbance though collapse may occur." The body fails to react and to make its struggle manifest. Fever is often lacking.

In the old, gallstones are common, colic rare, and the stone

may ulcerate through into the bowel without ever producing any pain; many other examples could be given.

Mental confusion is common even in the absence of obvious fever or toxemia. Lack of a will to live seems sometimes to determine a fatal outcome. An old person will sometimes simply fade into death during convalescence from some mild illness or after an apparently successful operation such as for cataract.

It is such deaths as these that seem almost physiologic—without definite pathological cause. It is of these that Warthin<sup>24</sup> wrote, deaths do occur from the “primary lesions of senility alone.” This is the most natural ending of life—and it is rare indeed! Warthin in his enormous experience only saw twenty-five such cases and in each of them he felt that death was in the last analysis due to myocardial inadequacy.

**Treatment of Disease in the Aged.**—And now finally let us discuss the treatment of disease in the aged. It is worthy of best attention—far more so than many a young physician is tempted to think. As Snowden<sup>25</sup> puts it: “Too often the tendency is to look upon the minor infirmities of old age as inevitable ones which the sufferer should bear in silence and the more acute illnesses as the beginning of the end.” Neither attitude is excusable—much can be done for the minor infirmities by a thoughtful physician and we all learn by experience what unexpected recoveries the aged may make from serious illness and how successfully they may undergo major surgery.

There is, it seems to me, a curious paradox in this matter of geriatric treatment which arises from the fact that the old react poorly to medicines but may stand surgery well. This means that we should be conservative in our medical treatment but not fear to take the risk of surgery when indicated. The danger is that we will employ too many drugs and from faulty timidity deprive our patient of a chance at surgical cure.

First, with regard to drugs. In general, it may be said that the aged absorb drugs slowly and that cumulative action is common. I have observed this especially with morphine and belladonna. Also it is true that sedatives may cause excitation

rather than the reverse and that they often bring about mental confusion or even delirium. Rolleston advises against morphine; Barker against chloral; even bromides may cause marked confusion. Whatever sedatives you employ—use a small dose and beware of delayed cumulative action. If your choice is morphine, it is well to combine with it a small dose of atropine to protect the respiratory center.

Belladonna is quite apt to excite the old and we are warned also to avoid the use of arsenic. Some even warn against digitalis although this is probably more a matter of dosage. In small daily ration it certainly seems to me to do much good; although I agree that in larger dose it may be definitely harmful.

It certainly seems reasonable that the aged organism can scarcely be expected to react to cardiac stimulants. The gist of the matter is contained in a favorite story of a very experienced physician at the Philadelphia General Hospital, to the effect that if your autopsy material is running low suggest to the interns that they are not being therapeutically active enough. For a few days the poor old wrecks of a city hospital's ward will show great signs of activity but then will come the final collapse.

Much the same reasoning applies to other diseases. I have seen an elderly diabetic made much worse by overenthusiastic dieting. Many old people have lived with their maladies for years and are more or less adjusted to this symbiotic state. The balance must not be too abruptly disturbed and remember always that the geriatric patient can only be restored to the state appropriate to his age—never to youth.

Often nursing is more important than doctoring. Often little matters determine the result. We must remember to adjust our efforts to the patient's long-established habits. For example, it is harmful to try with sedative to force an aged patient accustomed to five hours' sleep and the early awakening of the old to remain in sleep for eight hours until 8 in the morning. The old need rest and gentleness—but it is wiser

not to keep them in bed too long, for fear of hypostatic pneumonia and of insidious myocardial failure.

And, on the other hand, the aged stand surgery fairly well. Baily<sup>26</sup> put it as follows that the aged exhibit "unusual tolerance for serious major surgery," but as he quite properly states success depends upon preoperative study and postoperative care. He stresses the importance of short bed period and good cheer. Baily reports the results of major surgery in 185 patients whose ages range from sixty to eighty-four. The group included cases of appendicitis, intestinal obstruction, hernia, prostatic disease, cancer and biliary tract disease. The operative mortality for the series was 7.6 per cent.

Other reports of successful geriatric surgery include cataract operation<sup>27</sup> at ninety-six; gastric resection for carcinoma<sup>28</sup> up to seventy-eight; cholecystectomy<sup>29</sup> at eighty-six; operation on pharyngo-esophageal diverticula<sup>30</sup> in 3 cases all over seventy. But the prize report is that of Everidge.<sup>31</sup> The patient aged ninety-five wished his hernia repaired at the time of his prostatectomy because his truss interfered with his golf. It is this spirit which if the flesh is healthy leads to longevity. An interest in life is a primary requisite.

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## CLINIC OF DR. P. S. PELOUZE

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### THE TREATMENT OF THE COMPLICATIONS OF GONORRHEA IN THE MALE

OF first importance in gonorrhea is the prevention of complications, for with comparatively few exceptions, the complications of this disease do not need to be. Overwhelmingly they are precipitated by avoidable factors of patient conduct, hygiene or injudicious treatment. That this is so can be shown by a comparison of the number of complications in those individuals who have been subjected to these adverse influences with those occurring among gently treated, well-behaved patients. Such a comparison follows: an analysis of 750 cases, leaving out the question of posterior urethral involvement, which will be considered later, showed there were 207 complications at or before their first visit. While under gentle treatment with every effort made toward patient control, there were but 30 complications. A study of these 30 showed 19 cases of epididymitis, 16 of which followed gross misconduct on the part of the patient. In other words, there were but 11 complications in well-behaved patients. One of these was a case of arthritis immediately following the lancing of a para-urethral duct, and even this would not have happened if the procedure had not been done so early.

Thus we see that the number of complications depends mostly upon the three factors mentioned and, if we transfer the 16 cases of epididymitis occurring in noncooperative patients to the 207 present on admission, we find over nineteen and one-half times as many complications in the one group as



are found in the other. Regarding the presenting histories of those patients having the 207 complications there were few of them that reflected good conduct, good hygiene and gentle treatment.

Turning to the question of posterior urethral involvement, a close analysis of a smaller group of cases, 283, showed some very interesting figures. The purpose of this analysis was to get some idea as to the frequency of posterior infection under the plan of treatment used by the writer in regard to the time treatment was started. There were studied 100 consecutive patients presenting themselves for treatment before the sixth day of the disease and whatever number presented themselves at a later period of the disease but during the same length of time. This latter number was 183 cases. Of course many of these latter cases had received some type of treatment early in the disease.

Analyzing the 100 cases appearing before the sixth day it was found that 14 had a posterior urethral involvement on admission and 6 were noncooperative, leaving 80 who could be considered as good experimental animals. Of these 68 (85 per cent) failed to develop a posterior involvement while 12 (15 per cent) did.

Of the 183 patients presenting themselves on the sixth day or after, all but 12 had a posterior involvement when first seen and only 2 eventually escaped such disease extension.

In these latter figures it is outstanding that the percentage of posterior urethral infections with their concomitant prostatic involvement depends upon patient conduct and hygiene and the institution of gentle, careful local treatment prior to the sixth day of the disease.

Reverting to the prevention of the other complications, a study of the things done by patients and doctors immediately prior to their onset, gives us a large assortment of things that should not be done. The doctor faults center largely around the questions of lack of patient instruction, too early massage of the prostate gland, too forcible irrigations and the use of catheters, dilators and sounds. Patient faults are largely

matters of sexual excitement, alcoholic drinks, neglect and the trauma of self-treatment.

It is far from generally sensed that early, gentle treatment and increasing efforts to obtain and hold patient cooperation pay such enormous health dividends. Not only do they make the disease a milder and shorter one, but they take from the clinical picture at least 90 per cent of the unfortunate complications that do so much to make it a formidable health menace.

Today most physicians would express a belief that cure is dependent upon the patient's ability to engender the proper immunity responses. Despite this widespread belief there commonly are used many forms of treatment that one's wildest flights of imagination could not vision as immunity stimulants. And it is these forms of treatment that so commonly precipitate needless complications. Almost ceaselessly we dream of simpler forms of treatment, a state of mind that makes us avidly grasp at any new substance for which its originators claim simplicity and efficiency. We do not scrutinize the foundation upon which these claims rest, as we would in the treatment of almost any other disease, with the exception of the common cold, for which almost everyone will take almost anything. We largely have paid so little attention to what our efficient plans of treatment can do that one can bolster a report of value of his plan of treatment by the citation of some case histories that tell nothing and make it a story that carries conviction to the uncritical.

This, however, is not a discussion upon the treatment of gonorrhea but its complications, so let us take them up in the order of their frequency in the above mentioned series and briefly state more specifically how they can be prevented and how present thought says they should be treated if they do occur. There is no need that we talk more of posterior urethral infection, nor of its concomitant prostatic involvement unless the prostate is the seat of an acute swelling or a definite abscess formation. Otherwise both conditions are covered in any discussion on the treatment of gonorrhea itself.

## EPIDIDYMITIS

**Etiology.**—The view that the gonococcus usually reaches the epididymis by means of infected urine forced down the vas deferens is the safest from the standpoint of prevention. (The mechanism and reasons for thinking so are discussed fully in the writer's book on Gonorrhea in the Male and Female, W. B. Saunders Co.)

**Prevention.**—The avoidance of high pressure irrigations or injections and digital manipulation of the subvesical structures until late in the infection is of the utmost importance. It should be insisted that the patient with infected bladder urine carry out no heavy physical exertions unless the bladder is practically empty, that he make no effort to hold urine for long periods of time and that, if he is going to be foolish enough to indulge in the sex excitations of petting, he at least should avoid vesical distention while the session lasts.

**Treatment.**—The most effective methods for the treatment of epididymitis are a dressing that gives both support and pressure to the inflamed structures (a tight jock strap or bandage), rest in bed if the temperature is above 101° F., and the intravenous injection of 10 cc. of a 10 per cent solution of calcium gluconate daily for four or five days. Patients with lower temperatures safely may be kept ambulant.

Either local heat or cold may be used and if definite abscess formation can be made out an epididymotomy should be resorted to. Such abscesses are extremely rare. Epididymotomy also should be considered in patients exhibiting prolonged high temperatures. This procedure usually gives quick relief from pain, but as prolonged high temperature cases and abscess formation are the rarity, it seldom will have to be resorted to. The local application of ointments to the scrotum seems to serve no good purpose.

## ACUTELY SWOLLEN PROSTATE GLAND

**Etiology.**—The condition is usually the result of too early manipulations of the prostate gland. It sometimes occurs under the best of circumstances of conduct and treatment.

**Prevention.**—Let the prostate gland alone until the urethral infection has become decidedly inactive and then approach prostatic manipulations intent upon the utmost gentleness of procedure.

**Treatment.**—The best treatment for this condition is the application of heat to the gland in such a way that no trauma can result, otherwise epididymitis rather commonly is precipitated. Perhaps the safest way to apply this heat is by tying two catheters back to back so that one may serve as an inflow tube and the other as an outflow. Whatever type of apparatus is used should not be so constructed that it must be passed more than 1 inch beyond the anorectal junction. Unfortunately most of the rectal psychrophores must be passed much further into the rectum than this and are dangerous instruments to use under such circumstances. Water at 110° to 115° F. should be allowed to flow in and out for at least fifteen minutes twice in the twenty-four hours at first and then once until the swelling has subsided. Massage of such a gland should be withheld for three to four weeks or longer after it has become normal in size.

A rather common error is to be stampeded into the belief of definite abscess formation and advise operation at which only a quantity of dark blood is obtained. Even in the absence of abscess these cases often have a high temperature (103° to 106° F.) for several days and a high leukocyte count (15,000 to 20,000) which often persists for a week or two after the swelling entirely has subsided. The temperature, however, rarely stays high more than five days unless there is an abscess formation. At times it subsides and then recurs. Under these latter circumstances there usually need be no doubt about abscess formation when the gland is palpated per rectum. If abscess formation does occur it is a far better surgical procedure to evacuate it through the perineum than to incise through the rectum or break it into the urethra.

The general treatment is that of any other febrile state and one does well to avoid efforts toward intravesical medication until the gland has become normal in size.

## GONORRHEAL ARTHRITIS

**Etiology.**—As by far the large majority of our cases of gonorrheal arthritis occur among the poorly behaved, traumatically treated cases, it is safe to assume that the most potent precipitating factor is direct trauma to the infected structures. One should not assume, however, that just because a patient with gonorrhea has an arthritis that it is a gonorrheal arthritis, for it is not uncommon for patients with a previous history of focal infective arthritis to develop another attack at the onset of prostatic involvement by the gonococcus. In the absence of such a previous history the assumption of gonorrheal origin generally is warranted. To label arthritis gonorrheal simply because the patient once had gonorrhea is to lose sight of the fact that gonorrhea hardly ever lingers in the male more than a year or so, as well as the other far more common causes of arthritis.

**Prevention.**—The avoidance of direct trauma to the infected structures, of any surgical procedure however slight to these structures, insistence upon good patient conduct and resort only to the gentlest of treatment procedures, usually will practically obliterate gonococcal arthritis from the clinical picture.

**Treatment.**—If we may believe reports, and most of them seem trustworthy, it is in this complication that prolonged general hyperthermia registers its most striking success in the treatment of any phase of the disease. It is claimed that cure usually follows one treatment. The method, however, is not always easily available and many cases will have to forego its benefits.

When we turn to the question of other treatment we meet with a vast assortment of methods usually attended with the disappointments so common to such multiplicity. The most commonly used of these is rest in bed with restraint of the inflamed joint, usually by the use of a plaster cast. Some favor the intramuscular injections of foreign proteins. Some claim good results from small doses of gonococcal vaccines but the possibility of overwhelming the curative responses by vaccines

is a very real one. In the writer's opinion there is virtue at times in very small doses at the very beginning of an attack. Large doses used at any time probably account for some of the severe long-continued cases. The same applies with equal force to the Corbus-Ferry gonococcus filtrate.

It should be borne in mind that recovery from gonorrheal arthritis is just as much a matter of the building up of curative responses as is recovery from urethral gonorrhea. We have no quick, sure way to accomplish artificially what is really the patient's job. To overwhelm such a patient by the injection of gonococcal toxins or to roughly treat the lesions of the urethra and its adnexa during an attack of arthritis is to favor chronicity on the one hand and to favor both chronicity and extension to unaffected joints on the other. Seldom does one find in the entire clinical sphere of this disease a greater call for good judgment and gentleness of procedure.

#### FOLLICULITIS

**Etiology.**—Acute swelling of the urethral follicles is extremely rare in patients not subjected to traumatic treatment methods. Usually they follow the use of sounds, catheter irrigations or the instillating syringe during the course of gonorrhea.

**Prevention.**—The etiological factors readily show how the condition largely may be prevented.

**Treatment.**—It is far better to let nature deal with most cases of folliculitis rather than resort to efforts at intra-urethral surgical drainage. Almost invariably she does a better job, for resolution usually takes place. Local treatments to the urethra should be discontinued and heat applied two or more times a day, either by immersion of the penis in as hot water as can be borne for fifteen minutes, or a hot hip bath.

Where abscess formation really occurs and points toward the skin surface, incision should be made as soon as there is good reason to believe there is a true accumulation of pus. Such relief should not be withheld until the abscess has attached itself to the skin surface, for it usually spreads widely

before this takes place. In incising a follicular abscess care should be taken to make the skin opening far longer than is that into the abscess cavity and to pack the opening lightly with a gauze wick for a day or two. Otherwise the skin retracts and draws the external opening out of line with the internal causing subsequent drainage through a rather tortuous canal and greatly delaying recovery. To avoid the possibility of sinus formation all urethral treatment should be withheld at this time.

### SEMINAL VESICULITIS

**Etiology.**—This is probably much the same as is the case with epididymitis. There is little clinical evidence of real value to suggest that gonorrhea affects the seminal vesicles in more than 2 per cent of the cases. This also has been fully discussed in the author's book on gonorrhea and cannot be elaborated upon here.

**Prevention.**—This is the same as holds for the prevention of epididymitis.

**Treatment.**—Where true gonorrheal seminal vesiculitis is shown to exist, by virtue of the fact that the patient experiences a real increase of urethral discharge containing gonococci after each involuntary seminal emission, the treatment consists in vesicular strippings per rectum. These never should be done until the local condition has subsided to a point where such manipulations become reasonably safe. Such drainage of the vesicle should be carried out three times a week instead of the twice a week advised for prostatic treatments. During the acute stages, however, heat is most beneficial and it should be carried out in the same way as has been advised for acute prostatitis. Diathermy has no advantages over heat thus applied and is not without danger because of the larger instrument that must be passed into the rectum.

Surgical intervention, such as seminal vesiculotomy or vesiculectomy is needed upon only the rarest of occasions. The writer has never had to advise it for a case he has seen in either private or dispensary practice.

## COWPERITIS

**Etiology.**—This complication rarely occurs in the absence of urethral stricture, or high pressure irrigations or injections.

**Prevention.**—When resulting from the back pressure occasioned by urethral stricture it is usually in the type patient who has wilfully neglected the dilatations that have been advised, a thing not to be laid against the medical profession. On the other hand, the profession must share some of the blame for those few cases resulting from the forcible introduction of fluids into the urethra. That part of the picture we can obliterate by gentler methods of treatment.

**Treatment.**—The treatment almost always is surgical, for it is rare for a compound racemose of this type to fail to undergo abscess formation when infected by the gonococcus. Pointing, as a rule, toward the perineal skin surface on its own side of the bulbar urethra the condition usually is easy of diagnosis. Particularly is this so if grasped between the index finger in the rectum and the thumb on the external perineal surface.

Incision should be free and a small wick should be placed for drainage to prevent premature closure of the incision as the swelling subsides. In fact, it is well to keep up drainage for considerable time to avoid chronic infection of the gland. Chronic cowperitis sometimes follows infection without abscess formation. Such patients usually have a slight gonococcus-laden discharge for a long period of time. Normally Cowper's glands cannot be felt, so that any palpable swelling at the usual site of the gland should be considered pathological and treated. Frequently digital kneading of the palpable gland at the same time that the prostate is massaged is followed by cure. At times failure attends and it is then justifiable to remove the glands surgically, a procedure that presents little difficulty to either the surgeon or the patient.

## MARKED INDURATION OF THE CORPUS SPONGIOSUM

**Etiology.**—This rather common forerunner of stricture formation almost invariably is due to urethral trauma either



by instruments, strong chemicals, masturbation or sexual intercourse during the acute stage of the disease.

**Prevention.**—This is obvious.

**Treatment.**—The local application of heat as heretofore advised is our best mode of treatment. Otherwise no local measures should be resorted to until the swelling has softened. Sedatives and the usual measures for the prevention of erection with its attendant chordee also are indicated.

### LYMPHANGITIS AND DORSAL PHLEBITIS

**Etiology.**—These are almost always due to local trauma and are easily prevented by its avoidance. They are extremely rare in the usual run of office patients and far more common among the more poorly behaved group that attend dispensaries.

**Treatment.**—Practically always they clear up promptly on the use of heat and protection from further injury to the organ.

### INGUINAL LYMPHADENITIS

(Gonorrheal Bubo)

**Etiology.**—The milder grades occur in almost every case of acute gonorrhea. The more pronounced grades usually are found in the patients with lymphangitis, phlebitis, phimosis and paraphimosis.

**Prevention.**—This rests in the avoidance of external trauma to the penis and proper cleansing of the preputial sac.

**Treatment.**—As the condition hardly ever eventuates in abscess formation but usually subsides within a few days no treatment is needed.

### INFLAMMATORY PHIMOSIS

**Etiology.**—This is caused by the same things that determine the advent of phlebitis and lymphangitis and most commonly results from them. At times it is due to lack of cleansing of the preputial sac in the presence of urethral discharge and is associated with a balanoposthitis.

**Prevention.**—This is obvious.

**Treatment.**—The condition usually subsides rather quickly under the application of heat by penile immersion or the hot sitz bath and irrigation of the preputial sac with 1:5000 solution of potassium permanganate solution. Where the prepuce can be retracted the use of a mild antiseptic dusting powder is of great benefit.

If concealed ulceration is suspected a few days of heat and preputial irrigation frequently will restore conditions sufficiently for the retraction of the foreskin to make dark-field study, which is imperative for every penile sore, easily possible within three or four days. One should not hesitate to do a dorsal slit, or, perhaps, a cautery circumcision as few things are more important than the discovery of syphilis in its dark-field positive seronegative stage.

#### GONORRHEAL PARAPHIMOSIS

**Etiology.**—Almost invariably this is due to direct trauma to the penis in the presence of rather a small preputial meatus and its prevention is obvious.

**Treatment.**—The foreskin should be replaced as early as possible to prevent induration and ulceration at the point of greatest constriction. In order to do this the glans penis should be grasped by the gloved fingers of one hand, while the other hand is used to encircle the swollen, misplaced prepuce. Gentle, continuous pressure should be made upon both structures until about all of the swelling is gone. The parts then usually are easy to place in their normal positions. To prevent subsequent retraction it is well to pass a strip of adhesive plaster along one side of the penis, over part of the preputial opening in such a way as to make it smaller, but not occlude it, and then down along the other side of the penile shaft. This should be left on for several days. In the presence of neglected paraphimosis with much induration it occasionally is necessary to incise the constricting band on the dorsum of the penis. If ulceration has taken place it is wise to attempt to sterilize the surface by the application of tincture of iodine before in-

cision of the constriction. Ulcerations of the glans penis from prolonged penile constriction usually heal promptly upon the use of an antiseptic dusting powder. Before this is used, however, a dark-field study of the ulcer fluid should be carried out.

#### PARAFRENAL SINUSITIS

**Etiology.**—These glandular structures get their infection from the preputial sac and not the urethra. The condition is most common in individuals with profuse urethral discharge and a redundant prepuce. It probably is not preventable. Abscess formation almost invariably takes place causing a swelling just to one or both sides of the preputial frenum.

**Treatment.**—About the best way to handle this condition is to grasp the top of the swelling with a small mouse-tooth forceps and snip off most of the covering area with scissors. This leaves an opening through which it is easier to carry out local treatments, whereas a small incision soon shrinks so that the opening cannot be found. Starting the second day after opening, 5 per cent silver nucleinate or some similar solution should be injected into the gland channel daily if chronic gonococcal infection is to be prevented. For these structures, like the para-urethral sinuses, commonly harbor the gonococcus for months or years unless they are thus treated.

#### COMMENT

In the above citations of treatments one is likely to miss a number of things that have been rather widely vaunted for the various complications of this disease. Vaccines and the Corbus-Ferry gonococcus filtrate have been slighted intentionally as things more likely to produce complications than to promote their cure when once established. Diathermy, even in epididymitis, has lost most of its friends. General, prolonged hyperthermias in complications other than arthritis is hardly warranted. I have a report of fulminating suppurations in the only 2 cases of epididymitis one worker placed in his heat cabinet, and the other complications hardly merit such

treatment, if, indeed, it would benefit them. Just what such treatments would do for that fortunately rare gonorrheal complication, gonococcemia, remains to be answered.

The injection of foreign proteins in all stages of gonorrhea in the male and its complications, with the possible exception of arthritis, has lived its little hour and gone where most good Arabs go. The same can be said of a host of other things and largely we have returned to those things that gave even our forefathers good results. This is not without its rewards, not the least of which is an attractive simplicity of procedure in the place of uncertainty and confusion. Also, it is not necessary that one should impoverish himself by the purchase of paraphernalia that, though dramatic, largely are not needed for the treatment of either this disease or its complications.



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### THE MANAGEMENT OF CHRONIC PROSTATITIS

THE management of chronic prostatitis is quite often a problem that puzzles the urologist as well as the general practitioner.

The prostate gland is so situated anatomically that its normal drainage is mostly "uphill," contrary to the cardinal principle of "downhill" drainage for combating infection. The prostatic ducts and alveoli are lined with a single layer of columnar epithelium which is especially susceptible to infection and the external secretion, rich in lecithin, an excellent medium for almost any bacterial growth. Thus it will be seen that in prostatitis we are faced with the problem of treating not only an infection, but one that has been implanted in a most favorable soil. It may seem a trite statement to say that the treatment of chronic prostatitis depends upon the etiology of this infection but unless the many varied causative factors of prostatitis are evaluated and reviewed any haphazard treatment must be doomed to failure.

By far and large the greatest number of prostatic infections are postgonorrheal in origin. This ever prevalent disease affects from 75 to 85 per cent of the male adult population of the United States and is our third most prevalent infection, being exceeded only by the common coryza and measles. Gonorrheal prostatitis is always a complication of specific posterior urethritis. In gonorrhea the incidence of posterior involvement varies greatly with different clinicians. The limitation of gonorrheal urethritis to the anterior urethra

varies greatly according to different observers and to the type of cases treated. Dispensary patients usually have a tremendously high incidence of posterior urethritis due to lack of patient cooperation and also to the fact that daily treatment is not possible. In private practice the limitation of gonorrheal urethritis to the anterior urethra should show much more favorable results. Nevertheless there will always be an irreducible number of cases in whom a posterior involvement is inevitable.

The diagnosis of the early gonorrheal prostatitis should not be difficult. There is always an antecedent attack of specific urethritis accompanied by symptoms of dysuria, frequency, urgency or nocturia, all cardinal symptoms of posterior urethritis. Prostatic infection follows in every case of posterior urethritis. The gonococcus may be demonstrated in smears of the prostatic secretion of early prostatitis.

Here an important warning must be given as to when it is safe to massage or express secretion from a gonorrheal prostate. No digital manipulation should be attempted until the acute infection is entirely subsided and the voided urine is clear except for the presence of pus shreds. A safe method of avoiding complications is to withhold massage until the urine has been clear from ten to fourteen days and there is no reaction to posterior irrigation. Then the first attack on the prostate gland should be made with extreme gentleness, making no special attempt to obtain the secretion until it is seen that massage does not cause an acute exacerbation.

In "old" cases of gonorrheal prostatitis the discovery of the gonococcus is extremely difficult and there is always the probability that the specific organism has been overcome by an acquired immunity and that the infection is prolonged by a secondary bacterial invasion. Gonococcus carriers are rare in the male and persistent positive bacterial smears are usually the result of obvious clinical lesions.

The history varies greatly in prostatitis that is diagnosed from three or more years after an acute specific urethritis. There may be a period during which the patient indulged

liberally in alcohol and intercourse, having been pronounced cured of an original infection, then for no definite reason has a recurrence of prostatitis manifested by a urethritis or prostatic smear containing an excess of leukocytes. It is practically impossible for a host to the gonococcus to indulge in alcohol or intercourse without exacerbation of infection and any bizarre history indicates a lighting up of a chronic nonspecific infection or an untruth on the part of the patient, usually a married man.

It is difficult to demonstrate the gonococcus in prostatitis coming to treatment at a late period following the primary attack. Smears may be negative and cultures of prostatic secretion are unsatisfactory because other bacteria will outgrow and mask the gonococcus even if it is present. The complement fixation test may be of value but it is difficult to procure a satisfactory antigen and there is doubt concerning the period that this test is positive following the subsidence of specific infection.

Treatment of specific prostatitis should be begun with extreme caution and it is a safe rule that if doubt exists, then prostatic massage should be deferred. Prostatic massage accomplishes several things, including digital expression of secretion and pus, establishment of increased drainage and improvement in local circulation by relieving congestion.

The application of a mild antiseptic solution to the urethra is desirable in cases of recent infection. This may prevent a recurrence of urethritis from a new implantation of organisms expressed from the prostate gland. Potassium permanganate solution in strength varying from 1:8000 to 1:16,000 (1 to 2 grains in a quart of water) is quite satisfactory.

After voiding, the urethra and bladder should be irrigated with warm potassium permanganate solution two or three times and some of the drug be retained in the bladder by the patient. Massage should follow immediately and then the bladder emptied by voluntary urination to wash away the expressed pus and bacteria. Material for bacteriologic and microscopic examination may be obtained after massage.



Although the technic of prostatic massage is simple it might be well to remember that roughness will result in complications. Prostatic stroking should be done in the vertical plane and the midline touched only at the termination of a treatment and then but lightly to obtain a specimen. Massage using a horizontal stroke may force infectious material into the ejaculatory ducts. This often results in an acute seminal vesiculitis and epididymitis for which the physician alone is to blame.

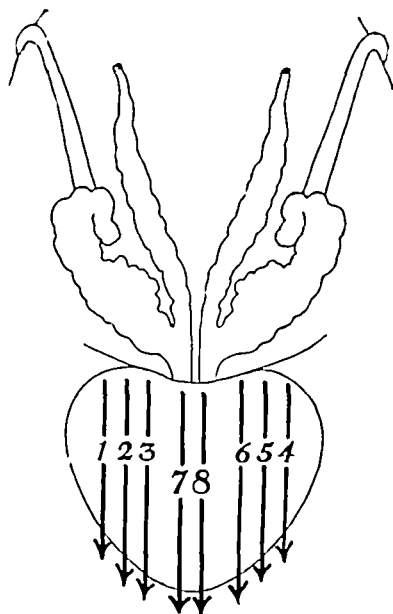


Fig. 2.—Direction of the stroking of the prostate gland. By leaving the midline strokes until last the discomfort is reduced to a minimum and is at the end of the treatment. (Pelouze, "Gonorrhea in the Male and Female.")

The extent of each treatment of course varies. Patient tolerance should be considered but in most cases no subjective discomfort is experienced after the first few massages. Each lateral lobe of the gland should be massaged until a definite emptying is felt which usually requires about ten strokes on either side.

Such treatment should be carried out twice a week. The importance of regularity should be impressed definitely upon the patient. Massage at weekly or longer intervals will never

cure prostatitis and more frequent treatment than at three- or four-day intervals may prolong the infection by the inflicted trauma. Fortunately gonorrheal prostatitis, under proper patient control and proper therapy, will readily respond and a cure should be effected in from three to four months.

The diagnosis of cure in these cases may be made by microscopic examination of the prostatic secretion. Specimens

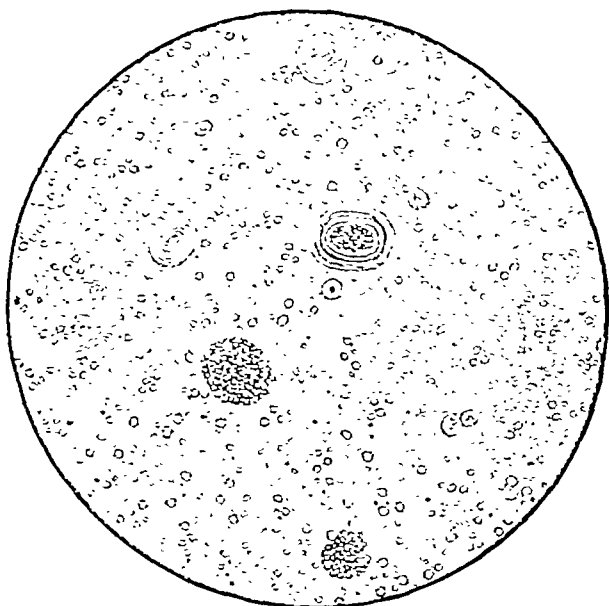


Fig. 3.—The microscopic appearance of normal prostatic secretion. The laminated bodies are corpora amylacea. The other large cells are prostatic granule cells. The next smaller are polymorphonuclear leukocytes in normal numbers. The remainder of the field is studded with lecithin bodies which are characteristic of this secretion. (Pelouze, "Gonorrhea in the Male and Female.")

should be examined under the high dry power of the microscope. Clumped leukocytes or an average of more than 8 to 10 per high dry-power field is an indication for further treatment. It is difficult to find the gonococcus in smears in the later stages of this infection but these organisms will not remain in the prostate gland without producing a leukocytic response. Therefore if no pus is found in the prostatic secre-

tion for three consecutive smears a diagnosis of cure may be made provided that other foci of infection are eliminated.

Vaccines are of no value in the treatment of gonorrheal prostatitis.

Short-wave diathermy has not had sufficient clinical trial for its proper evaluation. If heat that is controlled properly and not destructive can be limited to an infected gland some beneficial results might be secured. However, it must be re-

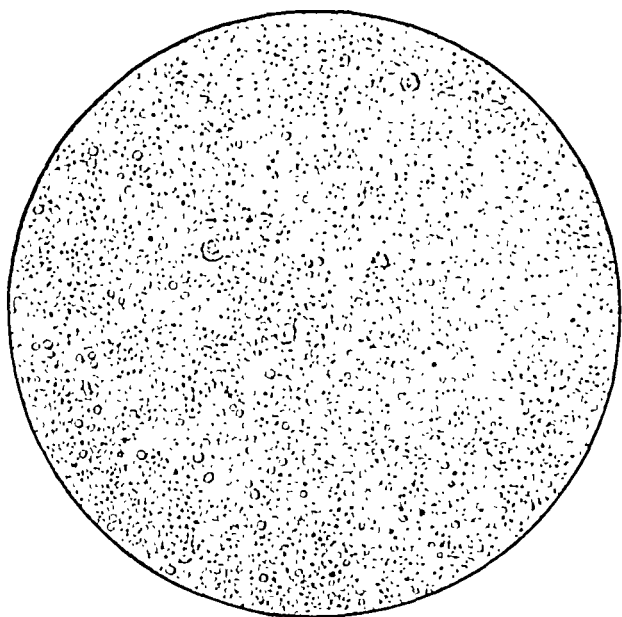


Fig. 4.—Prostatic secretion composed almost entirely of granular debris. A restudy within a few days generally reveals a large amount of pus. (Pelouze, "Gonorrhea in the Male and Female.")

membered that columnar epithelium such as found in the prostate gland has a lower thermal death point than that of the usual invading bacteria.

The nonspecific or nongonorrheal prostatic infections include a large group of mixed and often obscure etiology. Careful studies must be made and the treatment here often calls for long and varied therapy.

Commonest of all nonspecific infections are those in which

the prostate becomes secondarily involved and remains so until the original focus is eradicated. The symptoms may be those of focal infection such as general arthritis, spondylitis, iritis or iridocyclitis and almost any diseased condition from "spring fever" to brain tumor. In other instances symptoms point directly to the prostate as evidenced by chronic urethritis, pus shreds in the urine, or perineal and low lumbar pain.

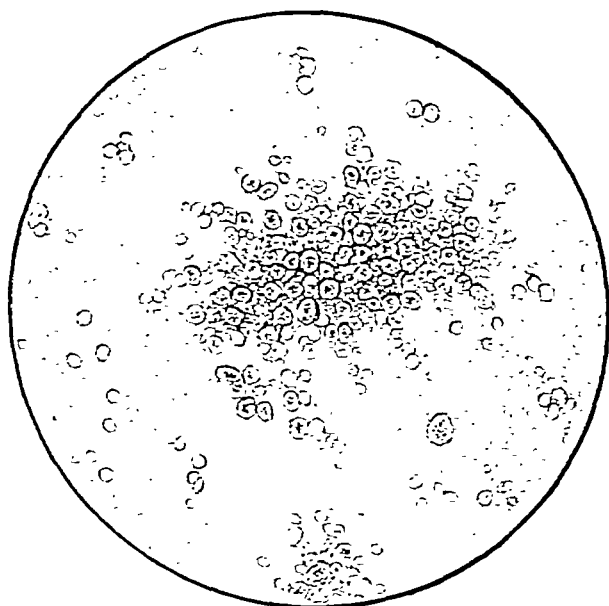


Fig. 5.—Prostatic secretion of a poorly draining infected gland. The scarcity of lecithin bodies in such secretions is very striking. As the leukocytes decrease in number these increase. (Pelouze, "Gonorrhea in the Male and Female.")

These statements should not indicate that prostatitis is the source of all disease, but that the study of any case in which focal infection might be suspected should include a thorough investigation of the prostate and its secretion. A study of cases in consultation practice will reveal that numerous patients have had exhaustive studies and prolonged treatment without benefit until chronic prostatitis has been diagnosed and cleared up.

A constant and usual finding in secondary prostatitis is that the gland will improve and that pus will diminish under treatment. However, a vacation from massage or a flare up of original focus results in reinfection. The very recurrence of a chronic prostatitis is evidence enough that it is a secondary infection.

Dental apical infection or the presence of nonvital teeth are often a primary focus of secondary prostatitis. The dental

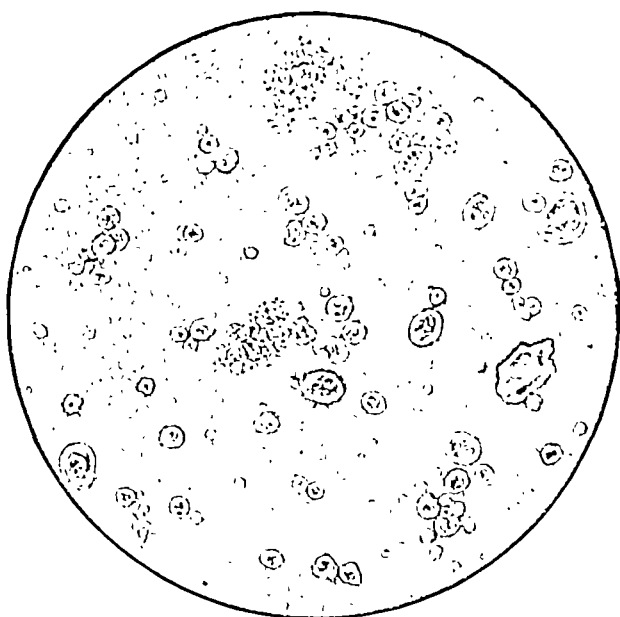


Fig. 6.—A prostatic secretion showing a slight tendency toward clumping of the leukocytes. Such a secretion is commonly seen and bespeaks poor prostatic drainage. It likewise is an intermediate picture evidencing improved drainage where previously there have been large clumps. (Pelouze, "Gonorrhea in the Male and Female.")

profession seem to be on the conservative swing of the pendulum. The radical tendency toward extraction of a few years ago seems to be now replaced largely by an attempt to treat abscessed teeth, rather than extract them. This may be successful in a few instances, but better and quicker results will be obtained in the presence of a prostatitis if all suspicious teeth

are extracted. Modern dental prosthesis is of such perfection that partial or complete dentures may be used and worn with comfort, thus overcoming any esthetic objections on the part of the patient.

If oral infection is allowed to remain, even under treatment, there is the possibility that it together with the secondary prostatitis may cause serious disease. Arthritis, iritis or any systemic complication may arise if any degree of infection persists.

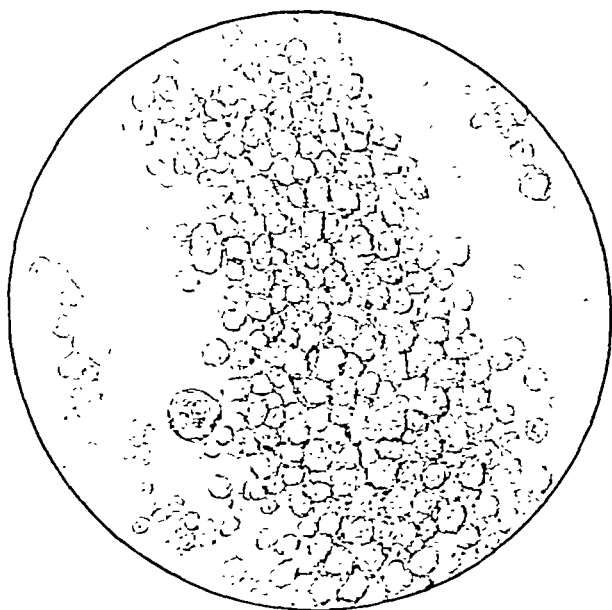


Fig. 7.—Prostatic secretion from a badly infected nondraining gland. The leukocytes are closely packed, old, and on the verge of disintegration. Lecithin bodies are almost absent. (Pelouze, "Gonorrhea in the Male and Female.")

Next in frequency as a cause of prostatitis is chronic sinus disease and chronic tonsillar infection. Not every one suffering from either or both of these diseased conditions has a prostatitis, but if this latter infection is present then the former should be viewed with suspicion. Tonsillectomy is an operation performed by many physicians and not always with the proper skill. Small tonsillar tabs are enough to harbor

infection and a complete examination is necessary even with the history of a previous tonsillectomy. Tonsillectomy, of course, is indicated even if the amount of tissue to be removed is small.

The problem of sinusitis is not so clearly definable, especially in a region such as this where a high majority of individuals, more marked in heavy smokers, suffer a varying grade of "Philadelphia nose and throat." Sinusitis of definite and recurrent type should be treated either by conservative or radical means. The opinion of the otolaryngologist should be freely asked and his advice followed. It is difficult for a general practitioner or a specialist in another field to gauge the extent and effects of sinus disease. If chronic prostatitis exists the sinusitis should be considered a primary factor and treated until its effect upon the prostate can be ascertained. There is no question that there are some instances of sinus or other infection that have no bearing, other than coincidental, upon the course of prostatitis. However, a therapeutic trial should be given especially if no other primary focus is present.

Less common primary foci for prostatitis include the gastro-intestinal tract, the gallbladder and the skin. These are unusual but should be considered if more obvious etiologic factors are not evident. Chronic constipation may be a factor owing to faulty elimination. Cholecystitis may be overlooked in prostatitis but should be eliminated as a causative factor. Dermatitis of the pyodermic type always should be investigated if associated with a persistent prostatitis.

The scope of this paper does not include a detailed study of the conditions enumerated in the preceding paragraph. The diagnostic measures needed to implicate any one of them are involved but attention is called to these condition in any resistant case of prostatitis.

Local conditions in the urethra may cause a persistence of chronic prostatitis, either by interfering with urethral drainage or by a continued irritation. Strictures, either congenital or acquired, may be causative factors. Strictures of the anterior urethra and as far posterior as the bulbomembranous

junction are practically all inflammatory in origin arising as the result of gonorrhea or from the injudicious use of too strong antiseptics which destroy urethral mucosa. This is always followed by its replacement with scar tissue which ultimately contracts to form a stricture. Strictures in the posterior urethra are congenital valves usually arising from the cristae galliae and may cause varying amounts of prostatic and urinary obstruction.

Anterior strictures may be diagnosed by a bulbous bougie or sound while posterior strictures are found by visualization through a urethroscope or cystoscope. Dilatation should relieve anterior strictures while fulguration is necessary to cut away the congenital valves.

Urethral irritative factors include the lymphoid bodies of Pelouze, polyps and papillomata. Repeated local treatment may be required to remove these conditions. Endoscopic applications of 25 to 50 per cent silver nitrate will destroy lymphoid bodies and polyps. Papillomata may be removed more satisfactorily by fulguration.

There are certain sexual aberrations that result in a prostatitis due to the result of prolonged passive congestion. Adult masturbators usually have a chronic prostatitis in proportion to their efforts in their favorite pursuit. Coitus interruptus, or withdrawal before orgasm, is a popular method of birth control. This procedure results in prostatitis following the passive congestion of incomplete orgasm. Too frequent intercourse and coitus prolongatus are conducive to prostatitis because of prolonged congestive trauma to the prostate gland. The remedy in all of these instances is obvious.

Many young men present themselves with a nonspecific urethritis that is caused by a low-grade prostatitis. Here there is often a history of excessive indulgence in alcohol and sexual excitement with or without intercourse. If no primary focus can be found these cases clear up upon prostatic treatment and correction of their social habits. The treatment of chronic nonspecific prostatitis should be directed along various lines. Original foci of infection should be searched for care-



fully, and eliminated by the proper therapeutic procedures. The confidence of the patient should be gained in order to ascertain whether or not he is indulging in any practices which might retard his progress. Cystoscopy or endoscopy is indicated in all instances in which treatment response is tardy.

Prostatic massage, as outlined previously, should be carried out regularly twice weekly. Intravesical irrigation is necessary only in those cases in which a urethritis is present. The time element varies greatly. It is usual for a nonspecific prostatitis to be more resistant to treatment than a post-gonorrheal infection and no patient should be given a glowing promise of prompt cure. In spite of ideal treatment and the location and elimination of a definite causative factor, the persistence of prostatitis may exceed the anticipation of both patient and physician.

Vaccines, either autogenous or stock, produce varying results, exactly as in any other infection. Autogenous vaccines are to be preferred and should be used only in small doses to avoid the establishment of a prolonged negative phase. Vaccines prepared from cultures of staphylococci seem to produce the least favorable results. Those made from streptococci, colon and diphtheroid organisms seem to produce beneficial results in certain cases.

Nonspecific protein therapy has not proved of value in the treatment of chronic prostatitis.

Reports vary upon the efficacy of direct injections of bacteriocidal substances into the prostate gland by both the trans-urethral and perineal routes. The author has had no success with injections through the McCarthy pan-endoscope and Dr. Sterling W. Moorhead (personal communication) states that injections via the perineum have not resulted favorably. Other operators have been more impressed by these methods and have reported large series of cases treated by a direct method. Here the end-results have been satisfactory but the methods used have required hospitalization of the patients.

**Summary.**—Gonorrheal prostatitis responds well to proper treatment if the patient is cooperative.

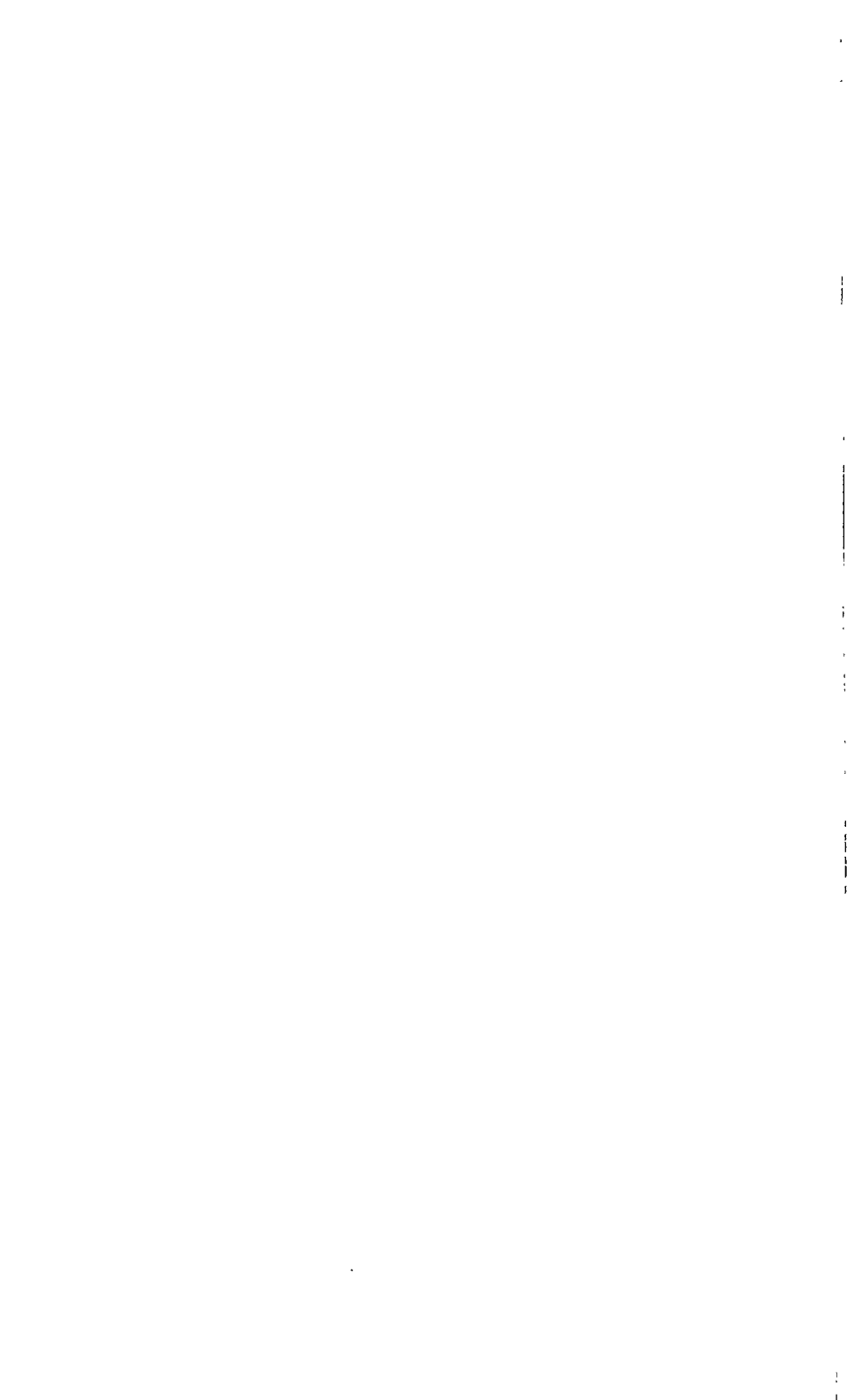
Many cases of prostatitis are due to secondary infection and will not respond unless the primary focus is eliminated.

Local pathology in the urethra may prolong a prostatic infection and should be searched for in recalcitrant cases.

The social and sexual habits of patients may produce or aggravate a prostatitis.

Chronic prostatitis requires a long course of treatment sometimes extending over a period of many months.

Some of the "newer methods" of treatment are not practical for general application.



## CLINIC OF DR. HENRY K. MOHLER

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#### THE DIAGNOSIS AND TREATMENT OF THE MORE COMMON CARDIAC ARRHYTHMIAS

THE common disorders of the cardiac mechanism, although but symptoms, have come to be considered as much in detail as are clinical entities. That they are but symptoms must not be lost sight of in any discussion of the subject.

The normal rhythm of the heart originates in the sino-auricular node, which lies at the junction of the superior vena cava and the right auricle.

The node receives branches from the vagus and also from the sympathetic nerve fibers, the former the inhibitory influence and the latter the accelerating force. A normal balance between these two nervous influences results in a regular heart rate of 65 to 80 per minute in the adult.

The cardiac irregularities are the result of either abnormal impulse production or conduction. The more common irregularities encountered are:

First.—Sinus arrhythmia.

Second.—Premature contractions, also referred to as extrasystoles.

Third.—Simple paroxysmal tachycardia.

Fourth.—Auricular fibrillation.

Fifth.—Auricular flutter.

Sixth.—Heart block.

Seventh.—Pulsus alternans, also referred to as alternation of the heart.

Proper methods of treatment of the arrhythmias can only be instituted after the nature of the disturbance of the cardiac mechanism of the heart has been identified. In a clinical study of the arrhythmia, auscultation over the precordium yields more valuable information than palpation of the radial pulse. In the majority of the cases a clinical examination will lead to a correct diagnosis.

An electrocardiographic study always will give accurate information as to the nature of the irregularity.

The type of disturbance having been recognized it is of importance to determine whether it arises in the heart muscle or if it is due to extracardiac factors, of a nervous, chemical or physical nature.

If the arrhythmia has its origin outside of the heart muscle the underlying etiological factors are sought and if located are treated to eliminate the disturbance of rhythm.

If there is a reduction in the capacity of the heart for effort, the activity of the individual must be regulated, if possible, so as to avoid bringing on the attacks.

The use of stimulants, as coffee, tobacco, alcohol in a fatigued or diseased heart may cause an irregularity which can be avoided by discontinuing the use of the exciting substance.

Sinus arrhythmia is a type of cardiac irregularity, common in childhood, in which the heart rate usually increases with inspiration and slows with expiration. Less frequently it does not follow closely the respiratory phase. The impulses for contraction originate in the sino-auricular node but are not discharged regularly as is the case in the normal sinus rhythm.

It is very common in childhood, usually disappearing as the individual enters adult age. Very occasionally the irregularity does not disappear with adult life but persists or recurs from time to time with an increased instability of the nervous system.

In the past and at present, without the use of the electrocardiogram the diagnosis is frequently incorrectly made. Before the use of the electrocardiogram this arrhythmia, as all

other irregularities, usually was regarded as a manifestation of organic disease of the heart and treated as such.

Speeding up the heart by exercise may cause the irregularity to disappear. Such a condition is usually functional in origin unless there is a history of disease previously having been present capable of permanently affecting the heart or because of the improper use of digitalis. In the presence of signs or symptoms of organic heart disease this disturbance may be present, but is functional in origin. The important factor to recognize is that no restriction or treatment should be instituted because of the presence of his irregularity alone.

This arrhythmia is so marked occasionally and may not follow the respiratory phase, that clinically it resembles either auricular fibrillation, heart block or premature contractions.

Slowing of the rate can be brought to the point of producing weakness, syncope and dizziness, by the use of drugs such as digitalis and quinidine sulphate in full doses, hence their use is definitely contraindicated. The use of atropine sulphate  $\frac{1}{64}$  grain (1 mg.) subcutaneously every three to six hours as needed, or ephedrine sulphate,  $\frac{3}{8}$  to  $\frac{1}{2}$  grain (20 to 30 mg.), or 10 to 15 minims or 1:1000 solution of epinephrine hydrochloride subcutaneously will usually increase the rate and cause the disappearance of symptoms which occasionally are due to the slow heart rate of sinus arrhythmia.

The very slow action of the heart in adults or children during disease or a surgical operation may be prevented by the hypodermic injection of 0.25 to 1 cc. of an aqueous solution of 1:1000 epinephrine hydrochloride. It is very unwise to restrict the activity of children in whom this form of cardiac irregularity occurs so commonly.

#### PREMATURE CONTRACTIONS (Extrasystoles)

The most frequent type of cardiac irregularity in the ambulatory adult occurs as premature contractions or, as they are also known, extrasystoles. Scarcely any individual fails to experience this condition at some time during life, even

though he is not conscious of its occurrence. The impulse for contraction in premature contractions arises outside of the normal center (the sino-auricular node). Organic disease of the heart often is not present. It must be excluded by a thorough investigation before assigning the cause of premature contractions as being functional in origin, or to a diseased condition arising outside of the heart or to toxic substances such as tobacco or coffee.

An individual may or may not be aware of their presence. Individual susceptibility is an important factor. The conditions of the nervous system, such as an instability brought on by emotional disturbances, susceptibility to tea, coffee, alcohol, tobacco, to fatigue, hyperthyroidism and intestinal disturbances are responsible or associated conditions. Premature contractions are often present in hypertension.

Premature contractions also have been termed, incorrectly, "dropped beats." Every second, third, or fourth heart beat at varying intervals may occur prematurely followed by a compensatory pause. These contractions are more likely to occur when the heart is beating slowly, during rest, and they frequently disappear with an increase in pulse rates such as produced by exercise. This observation usually will differentiate premature contractions from auricular fibrillation with a slow rate either at the bedside or in an ambulatory patient.

The occurrence of premature contractions in organic heart disease often precedes the onset of chronic auricular fibrillation.

If the premature contractions occur so quickly after a normal contraction so that the heart chambers have not been filled, then the premature contraction will not raise the aortic-valve leaflets. Under such circumstances no pulse effect is noted although the premature sound can be heard at the apex. A very slight pulse deficit then occurs and may be confusing if one does not think of it as occasionally occurring with premature contractions.

The treatment of extrasystoles consists in the elimination of the underlying diseased conditions and the removal or treat-

ment of other causes. The entire elimination or the use of smaller amounts of tobacco, tea, coffee and alcohol often aborts or prevents the occurrence of the irregularity.

The improvement of the digestion by discontinuance of overeating, eliminating highly seasoned food, the proper mastication of the food, the treatment of constipation, and by the use of physical exercises for those leading sedentary lives. The treatment of foci of infection has been successful in eradicating this disturbance.

Finally the use of sedatives, such as bromide of potassium, 10 grains (0.66 Gm.) three times daily, or the use of one of the barbituric acid compounds may produce magical effects.

Nothing will take the place of a period of rest for one hour once or twice during the day.

The use of digitalis is contraindicated unless congestive heart failure is present. Quinidine sulphate, 2 to 3 grains (0.13 to 0.2 Gm.) three times a day, has proved beneficial in eliminating premature contractions. They often disappear as quickly as they appeared, for no apparent reason.

#### SIMPLE PAROXYSMAL TACHYCARDIA

The etiological factors responsible for the attacks often go undiscovered and are those named in the discussion of premature contractions. Organic heart disease is usually absent. The person affected with the disturbance experiences a paroxysm of rapid heart action, beating regularly at a rate varying from 120 to 200 per minute. The attack starts abruptly and ends abruptly, and lasts from several minutes to several days. Occasionally an attack may continue from a week to six weeks. Frequently the longer attacks have been interrupted by a normal mechanism for a brief time only to have paroxysms recur again.

The rate of the heart at the beginning of the attack once set, does not fluctuate and is not affected by rest, exercise, posture and fever, such as does occur in ordinary tachycardia.

The rapid beating of the heart is usually readily observed over the precordium. The sensation of rapid cardiac pulsations



may be experienced, not only over the precordium but in some instances, more or less over the entire body.

The heart continues to beat rapidly and signs or symptoms of myocardial weakness do not appear until fatigue sets in, the onset which is determined more or less by the previous state of the heart muscle. A patient with mitral stenosis developing an attack of acute paroxysmal tachycardia would obviously be less able to effectively withstand an attack of myocardial fatigue, than an individual with a normal heart muscle.

Patients with prolonged myocardial fatigue as a result of paroxysmal tachycardia, become weak, develop an ashen gray color, congestion of the lungs, pulmonary edema and an enlarged liver. These signs and symptoms disappear very promptly with the cessation of the attack.

The treatment consists of therapy afforded during the attack and between attacks. Usually the paroxysms are of short duration and cease spontaneously and no treatment is needed.

The following plan of treatment is followed during the attack. Simple measures should be tried in the beginning after having endeavored to ascertain the cause of the attack. Inducing vomiting when the attack follows indiscretion in diet may end the tachycardia. The patient usually finds it more comfortable to be in a recumbent posture in quiet surroundings. An ice-bag over the precordium is helpful. Deep breathing with holding a long breath has been effective in ending many attacks. Counterirritation over the precordium by blistering, and mustard plasters is a useful remedial agent.

Occasionally a patient will find it more beneficial to walk or perform some slight bending, or leg- or arm-raising exercise and this may terminate the attack.

If these measures are unsuccessful in ending the tachycardia, then additional means should be instituted. These consist of stimulating the vagus nerves by making firm pressure first over the right carotid sheath in the neck for a period ranging from ten to sixty seconds. If pressure on the right side does not end the attack after one trial, then the same pro-

cedure should be undertaken over the left side of the neck. Pressure applied over the eyeballs with lids closed, one at a time, being firmly pressed inward may cause the attack to suddenly cease.

Quinidine sulphate by mouth in dosage of 2 to 3 grains (0.13 to 0.2 Gm.) every four hours has been effective in terminating the attacks. The idiosyncrasy to the drug should be tested before its use in full doses is attempted. Recently acetylbetamethylcholine has been used with success, beginning with the dosage of 20 mg. given subcutaneously every three or four hours.

In prolonged attacks, where congestive heart failure has resulted, bleeding and digitalization must be resorted to, but this rarely is necessary. Digitalis therapy as a general rule has not been successful in terminating these paroxysms.

When attacks occur frequently a careful history, a thorough physical examination and other tests should be obtained with a view of determining and eliminating the etiological factors.

The treatment between the frequently occurring attacks, for the purpose of preventing attacks, has not been uniformly successful. The continued use of 2 to 5 grains (0.13 to 0.3 Gm.) of quinidine sulphate three times a day has prevented frequent attacks, as has rarely full doses of digitalis.

#### AURICULAR FIBRILLATION

Auricular fibrillation is by far the most common irregularity found among the sick, of more serious import than some of the others and if recognized early and treated by the accepted methods responds in a very satisfactory manner, in a large number of the cases.

This disturbance is commonly associated with rheumatic fever manifestations (such as mitral stenosis), hypertension, coronary artery disease and hyperthyroidism, occasionally with unexplained conditions. It may also develop during acute infections such as tonsillitis, the grippe, acute bronchitis and pneumonia.

The diagnosis of this condition can usually be made at the bedside. The heart is irregular in rate, force and rhythm and usually rapid in the untreated case. Due to the number of small beats not reaching the radial artery there is a deficit in the number of pulse beats, being less than at the apex and this is known as pulse deficit. Adequate treatment causes the pulse deficit to disappear.

Exercise increases the pulse and heart rate and hence the degree of irregularity. Rest decreases these findings. The slower the heart rate when the patient is first seen the more difficult usually is the bedside diagnosis. An electrocardiographic examination may be necessary.

This condition is primarily one with no typical pathological picture by which it can be identified. In this disturbance, if it is of the chronic type (also designated as *pulsus irregularis perpetuus*, *delirium cordis* or the mitral pulse), the auricles are in a constant state of diastole, thereby not contracting as do the ventricles.

In the untreated case the heart ranges from 90 to 150 per minute. The guide to efficient treatment is the heart rate, not the pulse rate. The object sought for, in the treatment of chronic auricular fibrillation, is a heart rate, though irregular, ranging approximately from 70 to 80 per minute. Clinically the types of auricular fibrillation may be classified into (a) paroxysmal, (b) permanent or chronic type.

An attack of paroxysmal auricular fibrillation may suddenly cease if the cause is removed. Overexertion or excitement or indiscretion in taking food or alcoholic beverages, or in methods of living, especially in an older individual with arteriosclerosis, may bring on an attack. Rest with restriction in the diet and the treatment of gastro-intestinal disturbances may cause the irregularity suddenly to disappear.

In the paroxysmal type, digitalis and drugs, with like effects, probably have a tendency to prolong an attack. The drug most effective in this type is quinidine sulphate, 2 to 5 grains (0.13 to 0.3 Gm.) three or four times a day, if no signs of congestive heart failure are present.

Inasmuch as early hyperthyroidism may be accompanied by attacks of paroxysmal auricular fibrillation the possibility of it being responsible for the irregularity must be kept in mind even though the thyroid gland is normal in size and suitable treatment immediately instituted. A basal metabolic study will assist in the diagnosis. The chronic form seldom returns to normal rhythm and it is dangerous to attempt this step especially if congestive heart failure is present, because of embolic phenomena which may occur.

The purpose sought in treating chronic auricular fibrillation is to reduce the ventricular rate as counted by stethoscope over the heart to a rate ranging from 70 to 80 per minute. This can be accomplished in the ordinary case by giving 20 minims (1.2 cc.) tincture of digitalis or 2 grains (0.13 Gm.) of digitalis leaves three times a day. Ordinarily in one week with the patient at rest in bed with a favorable prognosis this result is achieved. Digitalis is continued in reduced dosage, the maintenance dose, to keep the heart rate within normal range.

If the patient comes under the physician's care in extremis and has had very little if any digitalis in the previous seventy-two hours, an intravenous injection of strophanthin,  $\frac{1}{120}$  grain (0.0005 Gm.), repeated in two hours and again in four hours, quickly may slow the heart rate. It is important not to slow the heart rate below 70 per minute or to give digitalis sufficient to produce heart block or coupling of the beats. This is dangerous and may produce sudden death.

Urgent symptoms of rapidly failing heart may require that the equivalent of 24 to 48 grains (1.5 to 3 Gm.) of powdered digitalis leaves be administered in from 1 to 6 doses during the first twenty-four or forty-eight hours.

Two conditions occur particularly in older persons. (1) Auricular fibrillation with a normal heart rate without symptoms. To treat this type of auricular fibrillation with digitalis is unwarranted, contraindicated and may prove fatal. (2) The other type case is one in an elderly person with marked congestive heart failure, heart rate 70 to 80 per minute with

or without the use of digitalis. To further reduce this rate is exceedingly dangerous. The prognosis in this type case is very grave. Absolute rest in bed and the administration of some opium preparation is indicated.

After a patient with auricular fibrillation has a heart rate of 70 to 80 per minute while in bed a maintenance dose of digitalis must be determined, which is the amount of digitalis required daily to keep the patient free from symptoms and enable him to be up and about if possible. By this method of digitalis therapy he may carry on for years.

In marked congestive heart failure with venous distention and cyanosis, blood letting may be a life-saving measure. Auricular fibrillation with hypertension may be benefited by the restriction of fluid and salt intake, rest in bed and the use of sedatives in addition to slowing of heart rate by digitalis.

The auricular fibrillation associated with hyperthyroidism disappears in a very large percentage of cases after surgical treatment of the thyroid gland. If no marked congestive heart failure is present and if auricular fibrillation persists after thyroidectomy quinidine therapy will restore a large number to normal rhythm.

The limitation of the patient's activity to his capacity for effort without symptoms must be insisted upon.

#### AURICULAR FLUTTER

Auricular flutter is not a very common occurrence. This type of irregularity is usually a chronic condition, lasting for months when untreated. Occasionally it occurs in short paroxysms. It is usually associated with organic heart disease, rarely is it a functional disturbance. Elderly individuals with diffuse arteriosclerosis are subject to this form of irregularity and it is very closely allied to auricular fibrillation. Patients with flutter often display periods of fibrillation. During hyperthyroidism attacks of auricular flutter may alternate with fibrillation.

The auricles beat at a rate of 200 to 360 per minute with the ventricles responding usually at a regular rate of 80 to 180

times a minute, every second, third or fourth auricular contraction being blocked. The rapid pulsations in the veins of the neck are often noticeable as compared with the pulse rate or the heart beats at the apex, which are much less in number. The rapid pulse may be regular or irregular, due to the ventricle responding only to every second or third beat at different intervals.

Its presence should also be suspected if there is an approximately regular heart rate of 80 or more per minute, with many more venous pulsations noticed in the neck than at the apex of the heart. Exercise may suddenly double the heart rate.

This disturbance is treated as outlined for auricular fibrillation with the use of digitalis. The tincture in doses of 20 minims (1.3 cc.) or 2 grains (0.13 Gm.) of powdered digitalis leaves is given three or four times daily until the heart rate is about 60 or 70 per minute. As the pulse rate is slowed, often the auricles begin to fibrillate. This should be a sign to discontinue digitalis therapy for twenty-four hours, during which time the heart rate usually returns to a normal rhythm. Auricular flutter may again return and the same procedure with digitalis therapy should be repeated.

Quinidine sulphate is a remedy used to eliminate flutter and only is recommended when digitalis fails, on account of the possibility that it may produce dangerously high rates.

The paroxysmal type of auricular flutter is treated by rest and digitalis, according to the method employed in the chronic type of flutter. All other measures used in the treatment of auricular fibrillation will be useful in the therapy indicated for this condition.

#### HEART BLOCK

The heart block to be described is that form that usually can be recognized clinically as partial and complete forms. It is a serious condition of the heart and commonly denotes rather widespread degenerative changes in the myocardium, unless it be congenital in origin. It may be temporary in

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#### HEART BLOCK

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nature, due to changes in conduction tissues or from overdigitalization or from acute infection and rheumatic fever.

Occasionally the changes are limited solely to the conduction system without any symptoms of myocardial insufficiency becoming evident for years. This has been so in block which developed years after an attack of diphtheria damaging the conduction tissue, with no or only slight damage to the myocardium.

Those recognized only by the electrocardiogram—prolongation of the P-R interval and bundle-branch block are not under consideration in this discussion. They cannot be recognized by physical examination.

When every second, third or fourth contraction of the auricle is not followed by a ventricular contraction, partial heart block results causing a slowing of the heart rate and pulse rate of 35 to 50 per minute. When the auricles and ventricles beat independently of one another with a rate of usually less than 40 per minute complete heart block is present.

In partial heart block the slowed ventricular rate may return to normal under the influence of atropine and exercise, usually not so in complete heart block unless it be of the acute type. An electrocardiogram is very helpful and is the only final test in doubtful cases of heart block.

The treatment of heart block is dependent upon the recognition of the associated conditions and etiology. If the heart block follows an acute infection, such as acute rheumatic fever, an attack of acute tonsillitis, diphtheria or syphilis, the treatment of these conditions with rest in bed may restore the normal mechanism of the heart.

If heart failure develops in a patient at rest in bed because of partial heart block, digitalis must be used in suitable dosage, 10 to 20 minims (0.66 to 1.33 cc.) of the tincture or 1 to 2 grains (0.06 to 0.12 Gm.) of the digitalis leaves three times a day. Even though the heart block may become complete atropine sulphate,  $\frac{1}{8}$  grain (0.008 Gm.) three times a day, has caused the block to disappear.

If syphilis is present it should be treated actively, although it frequently is not effective in the treatment of this block.

The slow heart rate of chronic block is not affected by fever, exercise and stimulants and this is a diagnostic point in differentiating it from a slow heart with normal mechanism.

The problems of treatment in complete heart block is often a great problem clinically, since in the condition the muscle as well as the conduction system is more frequently involved than in the conduction system alone. The complete block that follows acute coronary thrombosis often makes the prognosis more grave. The weak myocardium beating at half rate results in an inadequate circulation of the blood. Here absolute rest in bed, with the various drugs suggested may be tried as indicated by the condition or etiology to which it is related.

The Stokes-Adams syndrome in which convulsive features are present because of the pulse slowing to from 4 to 12 per minute requires the use of strychnine sulphate,  $\frac{1}{30}$  grain (0.02 Gm.) hypodermically, or 4 to 8 minims (0.25 to 0.5 cc.) epinephrine solution 1:1000 given intravenously. If the heart ceases to beat the immediate injection of 0.5 to 1 cc. epinephrine solution 1:1000 into the heart muscle directly through the chest wall may be a life-saving measure.

Barium chloride,  $\frac{1}{4}$  to  $\frac{3}{4}$  grain (0.015 to 0.045 Gm.) by mouth three or four times a day, has been reported to increase the irritability of the myocardium and hence increase the rate of contraction. This experience has not universally been confirmed by those who have used this drug.

Other preparations recommended are epinephrine in dosage of 0.5 to 1 cc. (1:1000 solution) given hypodermically, thyroid extract, strychnine sulphate, digitalis, the nitrites and vasodilators, such as the theobromine compounds, of which the following enjoy a wide reputation in the treatment of coronary arteriosclerosis, theobromine, 5 grains (0.3 Gm.), theobromine sodiosalicylate, 5 to 7 grains (0.3 to 0.5 Gm.) and metaphyllin, euphyllin, aminophyllin, theophylline,  $1\frac{1}{2}$  to 3 grains (0.1 to 0.3 Gm.) three times a day. Other compounds of theobromine are in use and may be helpful.

## PULSUS ALTERNANS (Alternation of the Heart)

Pulsus alternans is said to be present when the heart is approximately normal in rate with the presence of a pulse in which alternate beats are strong and weak. This is a result of a large or small quantity of blood being driven into the arterial system at alternate contractions of the heart. The explanation of this phenomena is not satisfactory. It is seen in conditions of exhaustion of the heart muscle, particularly so in the elderly or in those with chronic nephritis, chronic myocarditis, hypertension, coronary artery sclerosis and angina pectoris. The condition is serious because of the disorders with which it is associated. Its presence is the sign of an overtaxed heart. It calls for the reduction of physical activity to within the capacity for effort of the heart and the treatment of the associated and underlying conditions. Fatigue of the normal heart muscle, as in prolonged physical strain in athletics and in lengthy attacks of acute paroxysmal tachycardia, also are causes of pulsus alternans. Slowing of the heart rate by rest causes this disturbance in the normal heart to disappear without any permanent or unfavorable effects.

It is diagnosed by taking the blood pressure by the auscultatory method. The larger beats coming through at the beginning of the systolic reading are one half of the pulse rate and as air escapes from the cuff with the lowering of the systolic level by 10 to 20 mm. of mercury, weaker beats come through, finally totalling the full heart rate.

No particular drug therapy is indicated. The underlying cause must be treated by the intelligent use of digitalis. Providing adequate rest for the heart muscle is of prime importance.

The alternate weak and strong beats may be heard when listening over the heart, especially if the breath be held in expiration. Palpation of the radial pulse in an easily compressible artery may disclose alternate strong and weak beats. In pulsus alternans the pulse is regular in rhythm with equal spacing between each beat, while in bigeminal pulse the beat

occurs in pairs with a compensatory or longer pause between the paired beats. The electrocardiogram does not disclose this alternation but a pulse tracing will definitely record it.

It is an important finding when present, confirming the presence of a serious heart lesion, especially when confused with other conditions capable of causing severe dyspnea such as emphysema.



## CONTRIBUTION BY JOSEF B. NYLIN, M. D.

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### PHYSICAL EXERCISE IN CARDIAC CONDITIONS

IN Europe physical therapy has been for nearly a century an important part in the treatment of heart conditions. It is true that this method of treatment in some quarters has been used in too enthusiastic a manner, or sometimes too much as a matter of routine with correspondingly disappointing results. However, when scientifically employed, it has been of much benefit in a large percentage of cardiac diseases. In this country the medical profession has been rather slow in adopting physical measures as a means of treating disturbances of the heart. Lately, however, there has been a decided movement in favor of this particular therapy in treating these conditions. Illustrative of this attitude is the statement of Dr. William D. Stroud,<sup>1</sup> President of the Pennsylvania Heart Association:

"At the risk of being considered a 'drug nihilist,' the author believes that drugs are seldom indicated in the treatment of cardiovascular disease until such disease has begun to produce the earlier signs of congestive circulatory failure. By this statement we mean to suggest that digitalis, nitroglycerin, and other drugs supposed to improve the efficiency of the circulation or to remove symptoms of loss of the circulatory reserve are actually contraindicated in the earlier stages of cardiovascular disease. My thought is that as morphine masks the symptoms of acute appendicitis, so digitalis in the presence of breathlessness or nitroglycerin in the presence of substernal or precordial pain removes the circulation's only method of

notifying the patient that too great a burden is being placed upon it. Thus, if these drugs are able to remove the 'brake'—that is, breathlessness or pain—the patient continues to place more of a strain upon his circulatory reserve than it is able to carry, and congestive failure or coronary occlusion may soon develop. Physical therapy, on the other hand, may help to remove some of the burden and also build circulatory reserve so that the patient may return to a modified daily routine without symptoms. Of course, the symptoms may ultimately return with such severity that medication is the only form of therapy which will bring relief."

Of the various methods of physical therapy there are two which are particularly useful in the treatment of cardiac diseases; namely, (1) hydrotherapy, and (2) mechanotherapy, *i. e.*, treatment by mechanical means such as massage and exercises.

In this article it is our purpose to discuss briefly the latter of these two modalities.

When outlining the treatment for a patient with cardiac disease we must consider which measures are indicated in the particular stage of the disease; measures that aid the heart in its work or those that stimulate the heart to increased activity.

Rest lessens the work of the heart. Analogous to any other overworked muscle, a weak heart is thereby enabled to recuperate and thus to increase in strength. Physical rest should be combined with mental rest, the latter being fully as important, if not more so, than the former.

Measures that facilitate the flow of venous blood to the heart aid materially in the work of the heart. The most important of these measures are massage, passive movements, and respiratory exercises.

By massage the blood is forced out of the veins by the moving pressure of the operator's hands on the soft tissues. Furthermore, as Pemberton<sup>2</sup> states, the capillaries in the treated area are dilated by massage. As a result of these two factors the resistance to the blood stream is decreased, and therefore the work of the heart lessened.

Passive exercises, by which is meant movements performed in the patient's joints by some outside force, usually a masseur, also lessen the work of the cardiac muscle and help in unloading the burden of the heart. This effect is due to the fact that passive movements bring about alternately a lengthening and shortening of the veins of the exercised part. Thus more blood is alternately sucked into the veins and pressed out of them in the direction of the right auricle, the venous valves preventing it from flowing in the opposite direction. In order that the exercises may be truly passive in character it is absolutely necessary that the patient and particularly the moved part is perfectly relaxed; otherwise a resistive rather than a passive movement will result with entirely different effect on the heart.

Respiratory exercises act also as an aid to the heart by assisting the circulation from the right to the left side of the heart. These exercises further aid the heart in that inspiration increases the velocity of the venous blood stream, and expiration assists the cardiac muscles in filling the arterial system.

Measures that chiefly increase the work of the heart are active exercises, *i. e.*, movements in which the patient brings his muscles into action by his own volition. These exercises may be in the nature of either free or resistive movements. In the former the patient himself performs the movement without assistance or resistance of the operator; in the latter the operator gives resistance to the movement performed by the patient. A special method of active exercises sometimes used in the treatment of cardiac diseases is the so-called "Stokes-Oertal Terrain Exercises." This method consists of walking out-of-doors; in the beginning at approximately an even level, then as the function of the heart improves, at a gradually steepening incline.

In the insufficiency of the heart is not too pronounced, free active exercises performed slowly and evenly with sufficient rest between each individual movement often produce more aid to the heart than stimulation to increased work. The explanation of this effect is as follows:



Active exercises, like passive exercises, bring about an alternating lengthening and shortening of the veins, with the same physiological effect. In addition, however, active exercises aid the heart in ways not produced by passive movements. The capillaries of the working muscles dilate; the same dilatation takes place in the cutaneous vessels all over the body.<sup>3</sup> If the exercise is vigorous this latter effect is made visible by a general reddening of the skin. Furthermore, the contraction of the working muscles forces the blood in the veins of these muscles toward the right auricle. During the succeeding relaxation of the muscles the veins are filled again with blood. Finally, the respiratory movements are increased in depth and in frequency, and hence the pulmonary circulation is facilitated. The combination of all these factors brought about by active exercises naturally aids the heart materially in its work.

On the other hand, the increased amount of blood flowing into the heart, direct motor impulses, and probably chemical changes in the blood set up during voluntary exercise, all augment the activity of the heart. The more powerful the exercise, the greater is this increase in cardiac work.

Because of the afore-mentioned two-fold effect of active exercises upon the heart we are enabled by properly grading the exercises to produce a correct balance between the two opposite effects (*i. e.*, aid and increased work) so that we may meet the requirements of each individual case of cardiac disease. For this it is necessary, of course, that the heart have sufficient reserve power remaining to bear some increase in its work.

Let us now consider the therapeutic applications and the indications and contraindications of exercises in diseases of the heart.

Before a course of exercises, the patient should be thoroughly examined by the physician who, on the basis of his findings, then determines the type of movements, if any, suitable for the individual case. The physician should, in addition, carefully supervise the exercises throughout the whole

course of treatment. Medical supervision is particularly important during the first few weeks. During this period each exercise should, if possible, be under the guidance of the physician. Later on his presence during each performance of the gymnastic movements will be unnecessary, but he must keep in close enough touch with the case to be able to adjust the exercises according to the successive stages of the disease.

In the treatment of heart disease by medical gymnastics rest is a very important factor. Of course it would only aggravate the cardiac condition to treat with active exercises a patient whose heart has not sufficient reserve force to carry on his daily routine. Therefore we can see that more than the usual amount of rest, and, in some cases, a partial or total curtailment of the ordinary activity of the patient is a necessary complement to a program of gymnastic movements. As already mentioned, not only physical rest but mental rest is an essential element in the treatment of cardiac disease. Avoidance of responsibility, worry, and other emotional disturbances is therefore of great importance. It is difficult to either gauge the extent of these disturbances or relieve them if the patient continues to live in the environment which originally caused the mental strain. Hence the most satisfactory place for the treatment is in a hospital or sanatorium or at one of the various spas in this country or Europe.

During the execution of the exercises, the response of the cardiovascular system should be closely watched. If the exercises give rise to shortness of breath, palpitation, arrhythmia, or precordial pain, they should be discontinued at once or less vigorous movements substituted. Active exercises, even in a normal state of health, give rise to a temporary increase in the frequency of the pulse and a rise in blood pressure. If, however, the increase in the pulse rate and the rise in blood pressure last more than two or three minutes after the termination of the gymnastic movements they indicate that the exercises have been too strenuous for the heart. Less vigorous movements must therefore be substituted for them or they

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must be entirely discontinued until the strength of the heart has increased.

As to the indications and contraindications of the various types and methods of physical exercises for cardiac conditions it is obvious that milder measures must be employed for patients with pronounced deficiency of the heart than for those in which the heart still possesses a certain amount of reserve power.

When the heart is so insufficient that it is unable to maintain a fairly normal circulation even during rest, or when the lack of cardiac reserve power gives rise to severe dyspnea during rest, the patient should naturally be confined to bed. Under these conditions only rest, gentle massage, and passive movements in a limited number of joints are indicated. Active exercises are absolutely precluded. The massage should consist of stroking movements from the periphery toward the center, performed gently, smoothly, and with slow even rhythm. The hands of the operator should be so molded as to conform everywhere with the contour of the part over which they are gliding. Most patients in this condition respond favorably to general massage and derive much benefit from it. Occasionally, however, we meet with cases who do not tolerate massage of the whole body. In these cases the manipulations should be limited to the extremities until the patient has improved sufficiently to benefit from systemic massage.

Passive exercises have a somewhat more pronounced effect on the circulation than massage. The necessity of complete relaxation on the part of the patient during these movements cannot be overemphasized. Like massage, passive movements should be given with a slow even rhythm, and the moved part must be well supported by the operator for the exercises to be of a truly passive character. During this stage of the disease all passive exercises which are anatomically normal to the joints should be given to the wrist, elbow, ankle, and knee. Each movement should be repeated approximately five times in the joints of the ankles and wrist, and two or three times in the elbow and knee.

The treatment should begin with two deep respirations and should progress in the following order:

1. Massage to one of the legs.
2. Passive movements to the same leg.
3. Two deep respirations.
4. Pause, one minute.

This procedure is then repeated successively to the other leg, to each of the arms, and finally to the trunk. During the massage the patient must never be lying in a prone position as this position would prevent the patient from breathing freely.

When the most severe symptoms of insufficiency have been overcome, the pressure of the stroking movements should be increased. Furthermore, "kneading" to the arms and legs should now become a part of the treatment. This "kneading" is performed as follows: the operator with his thumb abducted as far as possible from the other fingers grasps the patient's extremity between his hands, and massages with gentle circular movements the arm or leg so that the soft tissues move with the excursions of the operator's hands. In this form of massage it is necessary that the "kneaded" parts of the extremity be only slightly lubricated, if at all, for otherwise the operator's hands would merely glide on the surface of the patient's skin, and the effect on the underlying soft tissues and the blood vessels contained in them would be so slight as to be of no or negligible therapeutic value.

The patient is now also able to bear passive movements in the hip and shoulder joints as well as passive flexion and extension of the trunk.

These exercises are described as follows:

- (A) Rotation of the extended leg to right and left.
- (B) Raising and lowering of the extended leg.

(C) Raising the thigh forward-upward toward the trunk with simultaneous flexion of the knee and hip joints, followed by lowering of the thigh with extension of the hip and knee joints. In this exercise the operator, standing at the side of the patient, grasps the sole of the patient's foot with one of his hands (if the right foot, the right hand should be used, if the



left, the left) and places his other hand back of and just below the patient's knee. With his hands thus placed he moves the thigh of the patient up and down.

(D) Abduction and adduction of the extended leg.

(E) Circumduction of the leg. In performing this movement the operator stands and places his hands as in exercise C. With the hand placed back of the patient's knee acting as a guide and the hip joint as a pivot to the movement, the operator moves the patient's knee in circles, upward, outward, and downward, while the foot moves in a horizontal, median plane, forward and backward. This movement is performed two or three times in one direction and repeated the same number of times in the opposite direction. At the beginning the circles described by the patient's knee are small in circumference. Later on, if the patient's reaction is favorable, the circumference can be increased.

Additional passive exercises for the arms are as follows:

(A) Rotation of the extended arm to right and left.

(B) Raising of the extended arm forward-upward, and then lowering it. There should be inspiration during the upward movement, expiration during the downward movement of the arm.

(C) Plane carrying of the arms. The extended arms of the patient are carried in front of the patient first inward, then outward—the arms being at shoulder level throughout the extended motion. Respiration as in B.

(D) Abduction and adduction of the extended arm. In the beginning the abduction of the arm should not exceed one half of the normal maximum range of this motion. Breathing as in exercises B and C.

(E) Circumduction of the arm. The operator stands at the side of the patient whose arm is flexed to a right angle. He grasps the arm in such a manner that his one hand holds the patient's hand, his other the patient's elbow. The arm is then moved in circles, two to three times in one direction, two to three times in the other.

In passive flexion-extension of the trunk, the operator stands at the right side of the patient and places his right hand under the left side and his left hand under the right side of the upper part of the patient's back. He proceeds to raise the patient's trunk to a vertical position, then slowly lowers it to the bed.

The various therapeutic elements comprising the treatment, *i. e.*, rest, massage, movements, and deep breathing, should succeed each other in the order previously outlined.

When the unilateral movements of the extremities cause no fatigue, the movements should be given bilaterally whenever that is technically practical. For example, instead of giving abduction and adduction to one arm at a time, both arms should be moved simultaneously. On the other hand, it would be almost impossible for the operator to perform adequately simultaneously circumduction of the patient's legs.

When the reserve power of the heart has improved so that the patient no longer suffers from shortness of breath during rest, but the insufficiency persists in causing dyspnea and abnormally high or prolonged pulse rate and blood pressure after slight physical exertion, active exercises constitute the most important element of treatment. The exercises, whether free or resistive, are performed progressively according to the amount of reserve power of the heart. It is of the greatest importance that the operator be constantly aware of the necessity of the correct proportion between the physical activity and the heart condition. Any definite routine or program of exercises cannot be given as they vary with each individual case; there must also be modification of the exercises in the event of unusual mental strain, lack of sleep, climatic conditions such as severe heat or humidity, which influence the condition of the patient. There are however certain definite rules which must be strictly observed in performing active movements:

1. There should be an interval of at least one hour between a meal and the exercises.
2. The progression should be from free active movements,

through a combination of alternately free and resistive movements, to entirely resistive exercises.

3. At first the patient should exercise only from a supine position. As the strength of the heart increases the exercises may be executed in a sitting position, and ultimately in a standing position. It is obvious that the several positions necessitate because of their very nature a limitation in the selection of exercises; *i. e.*, certain exercises cannot be performed from the horizontal position, others are impossible in the sitting position.

4. When the exercises are initiated they should be performed with one extremity at a time. When the reserve power of the heart permits, the extremities may move simultaneously, that is, both arms or both legs. At this time the trunk as well as the extremities may be exercised, but only certain movements may be permissible.

5. The exercises must not be repeated successively in the same part of the body. In the case of a unilateral exercise, a movement in one extremity should be followed by the same kind of movement in the corresponding extremity on the other side of the body. If the exercise is being administered bilaterally, a movement performed by the arms should be followed by a movement performed by the legs or the trunk. Although it is not permissible for an individual exercise to be repeated in the same part of the body during the treatment, the whole set of movements may be repeated if the patient's condition permits.

6. At the institution of the treatment, the exercises should be performed with a limited range of movement. The progression may be made gradually to the maximum range possible to the joint or joints involved in the movement.

7. Where the physician feels that the exercises should be administered with especial caution, an individual movement may be divided into sections: for example, the extended arm may be raised to an angle of 45 degrees, then rested, supported on the operator's hand; after a few seconds the movement may be continued to the shoulder level.

8. All exercises that expand the thorax should be accompanied by inspiration; all exercises that compress the thorax, by expiration. The patient should never be allowed to hold his breath during any exercise.

9. In certain types of cases, active exercises should be preceded by a brief general massage in order to facilitate the emptying of the veins and capillaries. This introductory measure is valuable chiefly at the stage of the cardiac condition when the reserve power of the heart is not yet adequate to permit the exercises to be taken in a sitting or standing position.

10. At the termination of the exercises the patient should take from 5 to 10 deep breaths while resting on his back.

Some additional regulations are necessary concerning the administration of totally resistive movements.

1. The operator should not grasp the patient's extremity, but merely exert pressure in opposition to the movement *in one direction only*. Otherwise confusion as to the intended direction of the movement is apt to arise in the patient's mind.

2. The force of gravity must be taken into consideration in offering resistance to the movements. This rule is especially applicable to exercises performed in a supine position. For example, in leg raising and lowering, less resistance should be applied during the upward movement than during the downward movement of the leg.

3. Each exercise should be followed by a pause of one to two minutes.

We will now proceed to a discussion of the treatment in cases where a somewhat greater reserve power of the heart exists. To this class belong, among others, patients who are able to engage in mild physical activities and who can take prolonged walks on the level without becoming short of breath, but who become dyspneic on participation in somewhat more strenuous physical activities or upon walking on an inclined plane.

At this stage resistive exercises constitute the most important element of treatment. More resistance should be offered to these movements than was indicated in the treatment

of patients in the group just discussed. Types of exercises demanding a relatively great increase in the expenditure of cardiac energy can be more freely employed, such as, trunk flexion-extension in forward-backward and lateral directions and arm lifting to above the horizontal level. However, the general rules and precautions outlined above concerning the administration of active exercises must be scrupulously observed.

Resistive exercises are contraindicated in certain pathological conditions. They are precluded in advanced arteriosclerosis because in this condition the blood vessels are unable to adapt themselves to the increased blood flow resulting from the augmented activity of the heart. Consequently the strain upon these vessels and the heart would become too great, and harm rather than benefit would result. A condition in which an acceleration of the blood current would tend to cause hemorrhage or increase a hemorrhage already existing is likewise a contraindication. Neither should resistance exercises be used in pronounced angina pectoris because of their tendency in that condition to bring on a severe cardiac attack. Naturally, the patient's general condition must be taken into consideration. It is obvious that all exercises are contraindicated in cases of pronounced neurasthenia and other conditions where rest is the supreme need.

Finally we will consider that group of patients who have a sufficient amount of cardiac reserve power to carry on the ordinary physical activities of their daily life and who experience shortness of breath, palpitation, and show abnormally high or prolonged rise in pulse rate or blood pressure only after relatively great physical efforts. Two methods of exercises are indicated at this stage, namely, resistive movements, and, under certain conditions, the so-called "Stokes-Oertel Terrain Exercises."

The resistive movements may now be employed with considerable resistance. In contrast to the rule in the stages previously described, each individual exercise may be repeated once or twice before the next movement is performed. As in

the other stages, it is often advisable to give the patient a brief general massage immediately before the exercises.

In the Stokes-Oertel method the patient walks out-of-doors with a slow, even gait. A deep inspiration is taken at every or every other step. In the beginning the walk should be short and should increase in length progressively as the heart improves. The walking must never cause dyspnea. If this unfavorable symptom should occur the patient must stop at once and rest until his breathing has returned to normal. Whenever possible benches where the patient may rest should be placed along the road. Furthermore, there should be markers at regular intervals the entire length of the path to indicate the distances to be covered. The walking exercises should begin on a horizontal level and increase gradually both as to distance and to incline.

The advantages and disadvantages of the Stokes-Oertel Terrain Exercises are described by Dr. A. Weber,<sup>4</sup> of Bad Nauheim, Germany, as follows:

"The Oertel cure, although possessing undoubted advantages, is being used less and less. By this method the physical activity corresponds in a very high degree with the requirements of the case. Undertaken in a systematic manner these exercises enable the heart to do its work with less effort than an untrained heart.

"Another great advantage is that these exercises are undertaken out of doors. Hence, the patient's general condition is benefited by the favorable influence of air and light. The psychic influence is equally beneficial. In a successful Oertel cure the steady improvement in functional capacity is much more apparent to the patient than in other therapeutic methods. Nothing makes a more favorable impression on the mind of a heart patient than when he finds that he is able to walk a path which he could not have attempted before.

"Oertel obtained many good results with his cure. Now-a-days, however, many physicians do not use his method because under certain condition it may cause considerable harm. One danger is that the patient often does not realize that he

Positions in which the exercise may be performed

Supine.	Sitting.	Standing.
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## ACTIVE EXERCISES.

Suitable for the treatment of cardiac conditions.

### I. Movements of the Leg

In the ankle joint:

1. *Ankle flexion-extension.*
2. *Foot rotation to right and left.*
3. *Foot circumduction to right and left.* If the patient is sitting the leg in which the movement takes place is crossed over the other leg.

In the knee joint:

4. *Knee flexion-extension.*

In the hip joint:

5. *Leg raising forward and lowering.*
6. *Leg raising backward and lowering.*



In supine or sitting position. Seen from above

7. *Leg raising forward-backward and lowering.*

8. *Knee abduction-adduction.* The knees are bent at right angles during this movement. In supine and sitting positions this movement can be performed bilaterally as well as unilaterally.

9. *Leg abduction-adduction.*

10. *Leg rotation to right and left.* If the patient is sitting he should sit close to the anterior edge of the seat of the chair, or with his legs supported in a horizontal position on the seat of another chair, as otherwise the performance of this movement is almost impossible.

In the knee and hip joint simultaneously:

11. *Knee raising forward-upward and lowering forward-downward.* In sitting position this movement should be performed with the patient in the same position as in Exercise. 8.



12. *Knee raising forward-upward and extension; knee flexion and lowering downward.* The patient first lifts his knee so that the thigh is nearly at a right angle to the trunk. From this position he then extends the knee. The knee is then flexed and lowered to its original position. In a sitting position the movement should start with the patient's legs supported horizontally in the same manner as in Exercise 10. During the movement of the active leg the other leg remains supported.

Positions in which the exercise may be performed.

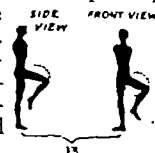
Supine.	Sitting.	Standing.
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## ACTIVE EXERCISES.

Suitable for the treatment of cardiac conditions.

### I. Movements of the Leg—Continued

13. *Leg circumduction.* With the knee bent at a right angle circular movements are performed upward, outward, downward, first in one direction then in the opposite. This is always a unilateral exercise whether the patient is supine, sitting, or standing. Furthermore, it cannot be performed as a resistive movement.



### II. Arm Movements

In the finger joints:

14. *Finger flexion-extension.*

In the wrist joints:

15. *Wrist flexion-extension in palmar-dorsal direction.*

16. *Wrist flexion in radial and ulnar direction.*

In the elbow joint:

17. *Elbow flexion-extension.*

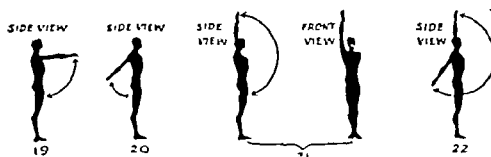
18. *Forearm rotation.* The arm is bent at a right angle in the elbow and held closely to the side of the trunk. In this position the forearm is rotated on its long axis to right and left.

In the shoulder joint:

19. *Arm raising forward and lowering.*

20. *Arm raising backward and lowering.*

21. *Arm raising forward-upward—lowering forward-downward.*



22. *Arm raising forward-upward, forward-downward-backward and downward.* Both Exercises 21 and 22 make a greater demand on the heart than Exercise 20 and should not be attempted unless the heart has a fairly good reserve power.

23. *Elbow flexion position arm abduction and adduction.* The arm is flexed at the elbow. In this position the arm is abducted upward to shoulder level, then lowered to the side of the trunk.



24. *Arm abduction-adduction.* This exercise which is performed with the arm extended makes a greater demand on the heart than Exercise 23.



Positions in which the exercise may be performed.

Supine.	Sitting.	Standing.
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## ACTIVE EXERCISES.

Suitable for the treatment of cardiac conditions.

### II. Arm Movements—Continued

25. *Arm rotation.* The extended arm held at the side of the trunk is rotated first in one direction and then in the opposite.

26. *Elbow flexion position arm circumduction.* With the arm flexed to an acute angle at the elbow the patient performs circular movements with the elbow first in one direction and then in the opposite.

27. *Arm circumduction.* The extended arm performs circular movements forward-upward-backward-downward, then in the opposite direction, i. e., backward-upward-forward-downward.



In the shoulder and elbow joints:

28. *Arm flexion-extension forward—flexion-extension downward.* The arm is first flexed upward at the elbow joint. It is then extended forward in a sagittal plane, so that the hand is brought straight forward at shoulder level. In the next movement the arm is flexed in the same manner and then extended downward to the side of the trunk.

29. *Arm flexion-extension outward—flexion-extension downward.* This exercise is performed in the same manner as Exercise 28 with the exception that the first extension is in an outward instead of a forward direction.

30. *Arm flexion-extension upward—flexion-extension downward.* Same as in previous two exercises except that the first extension is in a straight upward direction.

Exercises 28, 29, and 30 being composed of four individual movements increase considerably the work of the heart. In cases where the heart has a fairly good reserve power they can be performed, but if the heart is lacking in that reserve power, a rest should be given between each movement. Exercise 30 because of the arm extension above the head makes a greater demand on the heart than Exercises 28 and 29.

### III. Trunk Movements

31. *Trunk flexion forward-extension upward.* This

STANDING POSITION



DIAPHRAGM POSITION



movement should be performed in the hip joints and with the back straight. When performed

Positions in which the exercise may be performed.			ACTIVE EXERCISES. Suitable for the treatment of cardiac conditions.
Su-pine.	Stand-ing.	Sit-ting.	
			<p>III. Trunk Movements—<i>Continued</i></p> <p>in a standing position the patient should stand astride with his feet two feet apart. When performed in bed the operator should lift the patient to a three-quarter sitting position. From this position the trunk is raised actively by the patient to a nearly perpendicular position. During trunk extension the operator should give resistance to the movement until the trunk rests on the bed.</p> <p>If performed with the full range of movement this is a very strenuous exercise.</p>
—	+	+	<p>32. <i>Trunk lateral flexion.</i> The trunk is flexed in the lumbar and to a slight degree in the thoracic spine first to the right, then to the left. In standing position the patient stands astride; in sitting position his knees are about two feet apart.</p>
—	+	+	<p>33. <i>Trunk rotation.</i> From stride-standing or stride-sitting position the trunk is rotated on the longitudinal axis of the spine first to right, then to left.</p>
—	+	+	<p>34. <i>Trunk circumduction.</i> From stride-standing or stride-sitting the trunk is moved in circles, forward-outward-backward, first in one direction, then in the opposite. This is a very strenuous exercise.</p>

is undertaking too strenuous a task. A walk makes a far different demand on the heart in intense sunshine or when the atmosphere is excessively humid or a strong head-wind is blowing. If the patient becomes fatigued during his walk, the road home may result in profound exhaustion. Particularly dangerous is a terrain walk on which the patient is unaccompanied.

"In my opinion it is to carry caution too far to eliminate the Oertel cure because of these dangers. There is no objection to the terrain cure if its limitations are well understood. If the uphill climb is supervised by a trained person or by the physician himself, and if a conveyance is held in readiness at all times to bring the patient back from his walking exercise, there can be no danger.

"Indications are: cured or nearly cured insufficiency of the heart, obesity, myasthenia, and all types of severe anemia and kyphoscoliosis.

"Contraindications are: danger of embolism and apoplexy, aneurism, angina pectoris, and all pronounced congestive conditions."

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### PREVENTIVE ASPECTS OF CARDIOVASCULAR- RENAL DISEASE

CARDIOVASCULAR-RENAL disease, as the term is used in this discussion, is a condition which is characterized by the clinical features of widespread vascular disease and frequently the organ distribution of the vascular changes especially provides disturbed function of the heart, kidneys, brain, and eyes. The cause of this disease is not known, but it is closely related to hypertension and arteriosclerosis. Hypertension is only a measurable manifestation of this disease. In the light of present knowledge it seems unlikely that a single agent is responsible as a cause. Several factors seem to play a part in the cause and development of this disease. I shall refer mainly to those factors that seem to be important in the rôle of the physician as advisor to the patient.

Although there is considerable variation in the clinical behavior of this condition, three stages of development may be apparent; first, the potential cardiovascular-renal patient; second, the stage manifested by periodic and fluctuating degree of hypertension, or constant hypertension, but without symptoms; and third, the stage of well established hypertension with a variable chain of symptoms often referable to one or more organs or systems. In prevention of the disease as an entity, attention is especially drawn to the first two stages, while preventive measures in the third stage must necessarily concern complications. However, many factors which contribute to the development of the disease no doubt will also

influence some of the complications, even though the disease is well established.

Since knowledge at present is not certain enough to anticipate which member of a "vascular disease" family will develop clinical manifestations based on indications such as highly nervous temperament, frequent epistaxis in childhood, or signs of vasomotor instability, it is very difficult to evaluate, and advise the potential patient who may develop cardiovascular-renal disease. An inaccurate guess only contributes further undesirable and unnecessary anxiety to the patient's already possibly unstable psychic pattern. It seems possible that the reaction of blood pressure to a standard stimulus of cold reported by Hines and Brown<sup>1</sup> may be helpful in anticipating those members of "vascular disease" families who may develop vascular disturbance. Their studies indicated "that this vasomotor reaction follows an inherited pattern and that excessive or hypertensive type of reaction occurs in the families in which there is a hypertensive diathesis." Much further study is necessary before knowing how to interpret the findings for general application. However, the physician can not disregard his responsibility in watching over his "vascular families." O'Hare, Walker, and Vickers<sup>2</sup> in surveying the histories of 300 hypertensive cases found in 68 per cent of these patients a history of apoplexy, heart disease, nephritis, arteriosclerosis, or diabetes in one or more members of the family, while such history of familial vascular disease was present in only 37.6 per cent of a control group.

A very important group of patients is comprised of those who have developed definite hypertension but are without symptoms, and to these the physician must be a wise counselor and advisor rather than only a prescriber of drugs. Too often we must realize that we have very little scientific information on which to formulate advice. The four cases described below are representative of some of the individual types in this group and serve to elaborate the clinical application of some of the principles concerning apparently significant etiologic factors.

**Case I.**—G. R. B., male, age thirty-nine. Weight 167. School teacher. Has never had any symptoms referable to hypertension, although he has been known to have high blood pressure for at least four years, first observed during an examination for insurance. Has had no treatment for this condition other than an effort to avoid overweight. Does not use alcohol or tobacco. Because of a blood pressure of "over 200" found recently during a "health examination" he comes for medical advice. No family history of vascular disease other than his mother's sister died of a "stroke."

*Physical Examination.*—Stocky, sthenic type, not fat. Eyegrounds show very early vascular changes consistent with hypertension. No hemorrhages. No exudate. Heart moderately enlarged, the left border of cardiac dulness being 11.5 cm. in the fifth interspace. Accentuation of aortic second sound. No murmurs. Normal cardiac rhythm and rate. No signs of congestive heart failure. Blood pressure 220/120. After thirty minutes' rest lying down, 196/118.

*Laboratory Findings.*—Urine negative for albumin. No casts found but an occasional red blood cell was seen in the sediment. Highest specific gravity obtained in a concentration test was 1.026. Blood urea nitrogen 15 mg. per 100 cc. Urea clearance test showed 74 per cent of average normal function. Blood Wassermann negative.

**Case II.**—H. G., male, age forty-one. Weight 195. Physician. Has never had any symptoms definitely referable to hypertension, although during the past two years he had noticed ease of fatigue which he attributes to overwork and anxiety. Constipation for past five years. For past two years his blood pressure has always been found to be elevated, usually 160 to 180 systolic and 110 to 120 diastolic. Smokes excessively. Uses alcohol moderately. No family history of vascular disease.

*Physical Examination.*—Stocky, sthenic type. Obese. Eyegrounds show early vascular changes consistent with hypertension. No hemorrhage or exudate. Heart border-line

in size, the left border of cardiac dulness being 10 cm. in the fifth interspace. Accentuation of aortic second sound. No murmurs. Normal cardiac rhythm and rate. No signs of congestive failure. Blood pressure 174/118. After thirty minutes' rest lying down, 170/116.

*Laboratory Findings.*—Urine negative for albumin, and no casts or red blood cells found in the sediment. Highest specific gravity obtained in a concentration test was 1.030. Blood urea nitrogen 14 mg. per 100 cc. Urea clearance test showed 94 per cent of average normal function. Electrocardiogram negative except for slight left ventricular preponderance. x-Ray studies of heart and aorta showed very slight widening of aorta and very slight enlargement of the heart. Blood Wassermann negative.

**Case III.**—M. T., female, married, age forty-five. Housewife. Has never had any symptoms definitely referable to hypertension, although she has had constipation for many years and recently has noticed ease of fatigue, attributed to overwork and anxiety. Since age of fifteen has had occasional "sick headache" similar to those suffered by her mother. These have been less frequent and severe in the last few years. She has been known to have hypertension for past two years, discovered by "health examination." No treatment other than avoiding excess of protein and salt in the diet. Recently because of the fatigue has been resting more. Smokes moderately. Uses alcohol moderately.

No pregnancies. Menstruation irregular and scanty for past year. Occasionally has "hot flashes."

Mother died of diabetes mellitus at age of fifty, and maternal grandmother died of a "stroke" at age of seventy-six.

*Physical Examination.*—Tall and normal nourishment. Eyegrounds show very slight vascular changes consistent with hypertension. Heart moderately enlarged, the left border of cardiac dulness being 11 cm. in the fifth interspace. Aortic second sound moderately accentuated. No murmurs. Cardiac rhythm and rate normal. No signs of congestive

failure. Blood pressure 190/110. After thirty minutes' rest lying down, 186/108.

*Laboratory Findings.*—Urine showed a slight trace of albumin, occasional fine granular cast and red blood cell (not catheterized). The highest specific gravity obtained in a concentration test was 1.029. Blood urea nitrogen, 11 mg. per 100 cc. Urea clearance test showed 98 per cent of average normal function. Electrocardiogram was negative except for slight left ventricular preponderance. *x*-Ray studies of the aorta and heart showed very slight enlargement of the heart and some enlargement and elongation of the aorta.

**Case IV.**—E. B., female, married, age thirty-five. Housewife. Has never had any symptoms referable to hypertension, and the permanent high blood pressure was discovered first following an automobile accident about one year ago; said to have been "over 200." However, just before the birth of her only child five years ago she was told that she had kidney trouble and high blood pressure and her physician contemplated the advisability of interrupting the pregnancy a little early, but did not do so. She had no convulsions and the baby was normal. She was advised to have no further pregnancies. At this time she has no symptoms but seeks a periodic examination and medical advice as to any treatment for the hypertension.

Both her mother and a maternal aunt died of "strokes" at the ages of fifty-two and forty-nine respectively.

*Physical Examination.*—Moderately overweight. Eye-grounds showed retinal arteriosclerosis characterized by generalized attenuation of the retinal arteries, more marked peripherally. There was some accentuation of the reflex stripe. There were numerous punctate degenerative areas in the retina associated with pigment proliferation. This picture suggested a previous toxemia of pregnancy which was associated with retinitis and terminated in residual progressive hypertensive vascular disease. Heart not definitely enlarged. Moderate accentuation of aortic second sound. No murmurs.



Cardiac rhythm and rate normal. No signs of congestive failure. Blood pressure 220/110. After thirty minutes' rest lying down, 210/110.

*Laboratory Findings.*—Urine showed a very slight trace of albumin, but no casts or red blood cells were found. Highest specific gravity obtained in a concentration test was 1.028. Blood urea nitrogen, 10 mg. per 100 cc. Urea clearance test showed 77 per cent of average normal function. Electrocardiogram negative except for slight left ventricular preponderance. *x*-Ray studies of the heart and aorta showed very slight enlargement of the heart and a slight degree of dynamic dilatation of the aorta. Blood Wassermann negative.

By this time all four of these patients know that they have high blood pressure, are still essentially free of symptoms, and have sought advice about getting rid of the hypertension or in what manner to conduct their lives to arrest the condition and avoid or prolong the time of appearance of the complications later in life. All, by physical examination and laboratory studies, already show evidences of generalized vascular disease with some indication of incipient cardiac or renal involvement, although little or no manifestation of functional disturbance. Cases I and II are about the same age, and have essentially the same body type, although one is obese, the other is not. Their occupations are quite different. Case III represents the so-called "menopausal" type, who is not overweight. Case IV represents the female type still in the child-bearing period, already having vascular damage. The physician must act as advisor and his instruction to the patient will involve diet, the use of alcohol, tobacco, tea and coffee, exercise and occupation, the importance of mental and physical rest, infection, drugs, and in recent times the consideration of surgical procedures.

#### DIET

**Protein Restriction.**—It has become fashionable to restrict protein to some extent in the diet of such patients, the commonly accepted reason being the possible nephrotoxic

effects of protein or the by-products of protein metabolism. In the absence of renal functional impairment the usual diet prescription allows about the amount of protein necessary for normal body metabolism, perhaps as much as 1 Gm. protein per kilogram of body weight, or in the average patient 60 to 75 Gm. of protein daily. Clinical investigation in an effort to obtain guidance in protein restriction has produced rather conflicting findings, at least results rather difficult to interpret and apply to the individual patient. The work of Newburgh and his associates has been outstanding in support of the contention that by-products of protein metabolism are nephrotoxic. Protein feeding experiments were carried out on rabbits in the beginning.<sup>3</sup> An objection occurred in applying the results to man, because of the rabbit being herbivorous, and therefore not accustomed to animal food proteins, and also because the rabbit may be subject to a spontaneous nephritis not exactly comparable to the nephritis of man. Later studies by Newburgh and coworkers<sup>4, 5</sup> were made on white rats, showing that an excess of protein may cause urinary abnormalities in this omnivorous animal, and furthermore the development of these urinary changes were dependent upon the amount of protein and the length of time such diets were given. In investigating the element in the high protein diet that might be responsible for renal injury Newburgh and Marsh<sup>6</sup> by injecting various amino-acids intravenously into normal rabbits and puppies, demonstrated that arginin, aspartic acid, lysin, histidin, tyrosin, tryptophan and cystin were nephrotoxic. Jackson and Riggs<sup>7</sup> fed high protein diets, using casein and egg white, to rats over a period of ten to twenty months, corresponding to about one third of the rat's life, and were unable to produce any renal changes diagnostic of nephritis. Addis, MacKay, and MacKay,<sup>8</sup> also using rats, fed a diet containing 70 per cent protein or 1 per cent of cystin over about one third the rat's life, and were unable to demonstrate any pathological changes in the urine or kidneys. Although the experiments of these careful workers are not exactly comparable in every respect, one cannot feel at ease in

disregarding the positive results obtained by Newburgh and his associates. One should be cautious in applying findings in the experimental animal to the human; yet if an excess of protein or its metabolic by-products can produce renal injury in the rabbit, rat and dog it seems not improbable the same agent might be harmful to man. In interpreting such experiments one should not overlook the possible variation of vulnerability of the kidney to nephrotoxic agents in different species, and even in different individual members of the same species. Taking the urinary cast count as an index of nephrotoxicity, Brown and Englebach<sup>9</sup> have demonstrated that the rat may take much more mercury per unit of body weight than man before showing urinary changes, and an occasional rat may be especially resistant to mercury. Furthermore when the rat is given tolerant doses of mercury over a long period of time the kidneys may show very little microscopic evidence of nephritis, although the urinary-cast counts during life may have been increased.

In investigative studies in man again we find somewhat conflicting reports. Squier and Newburgh<sup>10</sup> fed high protein diets to patients with hypertension and observed the appearance of red blood cells and albumin in the urine. McCann and Keutmann<sup>11</sup> gave diets containing 75 to 200 Gm. of protein per day to four patients with latent or chronic active stage of hemorrhagic nephritis and observed no adverse effects. In spite of a liberal allowance of protein the hematuria was not increased and renal function as determined by the urea clearance test improved. However, in two of his patients an increase in proteinuria occurred when 150 Gm. of protein was given, but the renal function was not diminished.

**Fat.**—The possible influence of high fat feeding on the development of arteriosclerosis is not certain. Many have objected to the use of high fat diets in the treatment of diabetes in the fear of increasing this complication in these patients possibly already more susceptible to arteriosclerosis. However, those enthusiastic about high fat diets are far from convinced that arteriosclerosis is more prevalent among dia-

etics so treated for long periods of time. Much more clinical observation and pathological correlation will be necessary to settle this point. Most attention has been paid to cholesterol metabolic disturbance. Arteriosclerosis of the atheromatous type has been produced in rabbits by high cholesterol feeding,<sup>12, 13</sup> yet in the human an increased cholesterol in the blood has not been found uniformly in patients with arteriosclerosis, and, of course, many patients have advanced arteriosclerosis with no deviation from normal of blood cholesterol. Again species susceptibility must enter into this problem, as the rabbit seems especially vulnerable, and similar experiments do not produce similar results in many other animals. As yet evidence from feeding experiments is not convincing that disturbed lipid or cholesterol metabolism plays any significant part in human arteriosclerosis. Page, Kirk, and Van Slyke<sup>14</sup> in studying 16 cases of uncomplicated hypertension found no increase above normal range of concentration of total plasma lipids or of any of the lipid fractions.

**Salt.**—Allen<sup>15</sup> in 1920 advised greater restriction of salt in the diet of hypertensive vascular disease, and since then this has become a part of the routine advice to such patients. Further clinical investigation by others<sup>16</sup> has indicated that such rigid restriction is not necessary, and furthermore it is not clear that salt plays any significant part in vascular hypertension.

**Total Calories.**—The amount of food, and indeed the amount at any one time, probably is of as much importance as the excess of any one element. Reduction in weight is advisable for the obese and very large meals at any time are to be avoided because of the strain on the cardiocirculatory system. Although it is not clear that obesity causes cardiovascular disease, this condition appears especially prevalent in the overweight. Cases I and III should be advised to gain no more weight, and Cases II and IV should be advised to reduce. Potential cases of cardiovascular disease should be advised to avoid overweight.

The matter of diet instruction demands a great deal of

time from the physician, and in most instances it is not scientifically accurate, and frequently the patient cannot or does not adequately carry out even more liberal requirements. In the light of present knowledge the following instructions in diet will satisfy most clinical indications: (1) carbohydrate, fat, and total caloric intake compatible with normal weight; emphasis on small meals; avoidance or reduction of overweight. (2) Protein restriction to avoid excess, in the average case 60 to 75 Gm. daily providing the metabolic need. (3) Restriction of sodium chloride to avoid excess; this is difficult for the patient to measure, and usually is satisfactorily met by the instruction of "no added salt." (4) Studies in water balance rather point to the advisability avoiding excess of total fluid intake, about 2000 cc. daily being satisfactory for most patients.

#### TEA, COFFEE, ALCOHOL, TOBACCO

There is no convincing evidence that any of these agents cause hypertensive vascular disease and any contribution they make to the clinical picture is probably secondary. Therefore, forbidding their use as a preventive measure acts only in avoiding secondary effects, which vary widely in different individuals, some being more susceptible than others. The restless, nervous patient who is especially sensitive to caffeine will do well to avoid tea and coffee because of his nervous system rather than because of his cardiovascular apparatus. While alcohol probably does not cause cardiovascular disease the effects of alcohol make any more than its very moderate use highly inadvisable. The possible influence of tobacco on the functional capacity of the heart and the causation of angina pectoris in some individuals indicates a caution to any other than its very moderate use in these cases.

#### THE NERVOUS SYSTEM, OCCUPATION, REST, EXERCISE

The mechanism of the nervous system in the regulation of blood pressure has been investigated by many workers in recent years. So much information is available that correlation

and application of it to clinical problems is in a state of confusion. From the nervous system aspect the blood pressure level seems to depend upon a balance of the pressor influence of the sympathetic vasomotor component and the depressor influence of the parasympathetic vasomotor component. A disturbance of this balance favoring elevated blood pressure might be due to increased pressor effects or decreased depressor activity. A comprehensive understanding of this whole mechanism implies the relationship of many variables some of which are practically intangible. Nervous temperament, psychic pattern, emotional stress and strain, the nature of one's occupation, mental rest, the degree of equanimity concerning the unpleasant things in life, recreation, and even constitutional pattern, and the endocrine system, all enter into the final result of this balance mechanism. In the age group represented by the above cases occupations are likely already chosen and adequate training obtained, so that advising change of occupation should be attended with caution especially if livelihood is jeopardized. More often it is a matter of the patient adjusting his nervous mechanism to look upon the vicissitudes of his occupation with more equanimity, or lessening the nervous and mental load in some way or having more frequent rest periods and vacations. If one could recognize the potential cardiovascular case, one might be justified in advising some particular type of occupation for which he should train; at present it would be difficult to choose such an occupation, because we hardly know what the specifications should be. In advising patients we mention an occupation as free of nervous and emotional stress and strain as possible, and not too strenuous from a "muscular work" standpoint. Yet there seems to be every reason for such patients to have adequate exercise as long as there is no impairment of cardiac function. The patient in some way should realize that the exertion attended by dyspnea or precordial discomfort, or indigestion, is beyond wise tolerance. Adequate rest and sleep at night should be insisted upon, and frequently regulated rest periods during the day are advisable.

## INFECTION

It is difficult to evaluate the incidence of infections in past histories of cardiovascular cases. Walker and O'Hare<sup>17</sup> in surveying 400 cases of hypertension and 400 control cases without hypertension found no indication that previous infection played an important part in the cause of hypertension. During active infection of certain types, blood pressure may be elevated, in other types it may be lowered. No doubt the involvement of the kidney, as in streptococcic infections, or the adrenal in certain acute infections is an important factor in immediate blood pressure changes. In an occasional case the removal of a focus of infection lends a very favorable influence on an existent hypertension. The decision regarding removal of or attempting to clear up foci of infection should be reached in the same way in the hypertensive as in any other patient; it is the logical thing to do, but caution is urged in anticipating preventive or curative effect on cardiovascular diseases.

## DRUGS

Little need be said here about drugs as preventive treatment, since at present we have no known drugs that actually prevent this disease. The drugs in use are numerous, yet carefully controlled clinical investigation has not indicated convincing evidence of their efficiency in significant permanent lowering of blood pressure when employed in usually safe clinical doses. Most of the drugs referred to are used in treatment after the disease manifests symptoms. Recently the report of Barker<sup>18</sup> has revived an interest in the use of potassium or sodium thiocyanate in the hypertension of shorter duration in young individuals. The administration of this drug, to be entirely safe, must be carefully controlled by blood thiocyanate determination. While such cases as described above might be considered for this therapy, there is no evidence of thiocyanate being a preventive, and the hazard of toxicity makes its use in general inadvisable. The possible relationship of the endocrine glands to hypertension is brought up in Case III in that the patient is in the menopause. Al-

though the ovaries, pituitary, adrenal or thyroid may have some influence on cardiovascular-renal disease there is no convincing evidence that available substitution endocrine therapy has significant preventive influence on the condition. On the whole sedatives, such as phenobarbital, are likely to be more helpful because of their influence in quieting a responsive nervous system.

### SURGICAL TREATMENT

In recent years much attention has been called to various surgical procedures involving the sympathetic nervous system. Recently the results obtained by Peet<sup>19</sup> and his associates in performing greater splanchnic nerve trunk resection has seemed encouraging, and especially so since most of his patients were in an advanced stage. However, experience with this kind of treatment must be considered still in the developmental and experimental stage. The criteria for suitable selection of cases are not established, and since knowledge concerning the sympathetic nervous system is in such a state of incompleteness and confusion, a very conservative attitude should be displayed in advising cases similar to those described above.

### PREGNANCY

Pregnancy provides a great hazard to the hypertensive woman, and the avoidance of pregnancy or its interruption constitute most important preventive measures in such patients as represented by Case IV. The observance of this principle may give these patients years of useful and comfortable life. Eyeground examinations are of the greatest importance in these cases. Hallum<sup>20</sup> has pointed out that if retinitis occurs as a part of hypertensive toxemia before the twenty-eighth week of pregnancy the patient is almost certain to develop permanent vascular-renal injury.

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### INCIPIENT PARKINSONISM: DIAGNOSIS AND TREATMENT

PRIOR to the advent of acute epidemic encephalitis twenty years ago and its subsequent chronic ravages within the central nervous system, paralysis agitans occupied a quiet reserved place in the organic neurological scheme of things. It cropped up every once in a while in the latter decades of life and was recognized by the characteristic postures, attitudes and pill-rolling tremor. Its inception was not spectacular, its course insidiously progressive with increasing motor disability and tremor, hence the name paralysis agitans. Occasionally one would choose the name of Parkinson's disease in preference to the word paralysis out of respect for the unfortunate victim's feelings. Thomas Parkinson, English physician, formulated the symptom-complex of shaking palsy in 1817. For many years it was considered to be a functional disturbance of the central nervous system and treated as a neurosis until the pathological involvement of the lenticular nuclei was recognized and well established. It has been considered to be an idiopathic disease with premature disintegration of the ganglion cells of the globus pallidus except for the occasional case occurring in cerebral arteriosclerosis with softening in the region of the basal ganglia and in rare instances of tumor formation and syphilis involving the same area of the brain.

Much to the surprise and bewilderment of clinicians the great pandemic of influenza and the shortly following epidemics of acute encephalitis left in its wake numerous victims

with nervous manifestations suggesting paralysis agitans, yet differing in some respects either in the absence or predominance of one or the other characteristic features of paralysis agitans. Hence the term "parkinsonism" was applied to these postencephalitic cases. For a few years the diagnosis of postencephalitic parkinsonism was made only when the patient with rigidity and tremor gave a history of having had an attack of acute epidemic encephalitis. With increasing experience it was soon learned that the chronic manifestations of epidemic encephalitis could develop without a recognizable antecedent attack of the acute form. The incidence of the parkinsonian syndrome rapidly increased and observers became acquainted with a great variety of combinations of symptoms, some more or less fragmentary, until the symptom-complex was being diagnosed on the basis of a few fragments of the previously required diagnostic whole.

Aside from the exceptional type of acute parkinsonism, the development of the disease is usually insidious and one may correctly speak of the very earliest stage in the development of the syndrome as incipient parkinsonism. For obvious reasons the clinician strives to perfect himself in recognizing all pathological processes or clinical conditions in their incipient stages and it is with this in mind that the present paper is written. In preparing a digest of the initial symptoms and signs of the incipient stage of parkinsonism 100 private case records were selected representing patients varying in age from three to fifty years. Only 57 per cent of the patients either gave a history of having had sleeping sickness or described an acute illness strongly suggestive of that disease. Of the other 43 per cent a number of patients made mere mention of having had the "flu" or not at all. Complete recovery from the acute disease is frequently reported but just as often the patient is left with one or more residuals such as a change in the sleep rhythm from complete inversion (nocturnal insomnia and diurnal somnolence) to simple restlessness at night; ready fatigableness, exhaustibility of concentrative powers, fluctuation of emotional tones or a group of physical and mental symp-

toms constituting a veritable psychoneurotic state which may last many months to several years. This is the interval period between the acute attack and the appearance of early parkinsonian manifestations, or it may constitute what might be called the period of invasion when the disease begins without an acute attack of epidemic encephalitis, *i. e.*, the subacute and chronic forms.

**Modes of Onset.**—In a small percentage of cases the parkinsonian state is recognized immediately or shortly after the patient's recovery from the acute attack of epidemic encephalitis. It is usually an incomplete picture of the typical syndrome consisting of a change in the individual's facial expression variously described as fixed, blank, stary, or expressionless; the motor activities are generally slower than the patient's former normal behavior particularly in the field of the automatic associated movements such as the swinging of the arms in walking, the manner in which he sits down on and arises from a chair. These individuals are often unaware of the change in their appearance and motor behavior patterns, but friends and relatives immediately recognize the change and correctly describe it as being "a general slowing up." There are those who are keenly aware of the change themselves and note that they do not blink so often as they formerly did, that their arms do not move from the sides when walking and speak of feeling stiff, awkward and incapable of responding quickly in a motor sense. This general hypokinetic state may be associated with a feeling of fatigue, weakness or tiredness and the patient may attribute slowness of action to the latter with the reassuring thought that it is only a part of the temporary convalescent period. To this clinical picture may be added hypersomnolence with or without nocturnal insomnia, or intractable insomnia without the slightest suggestion of diurnal somnolence. The hypokinetic state of the lingual and throat muscles, insufficient to produce conscious dysphagia, accounts for the accumulation of saliva in the mouth with drooling when the patient bows his head or on the pillowcase at night.

One may expect to encounter the above picture in all degrees of progression yet without a suggestion of tremor in any part of the body. On the other hand, the first symptom of the parkinsonian state may be tremor without obvious slowness of voluntary motor activities or alteration in the automatic associated movements. On returning to his normal routine after recovering from the acute attack, the individual may notice the development of a fatigue tremor in one limb, upper or lower, soon becoming more persistent, more troublesome and eventually constant. The tremor in the hand, for instance, may appear when the limb rests in an awkward position or when using the member for fine manual acts such as writing and sewing. In the lower limb it may appear only when that leg is crossed over the other knee or when the foot is so placed on the floor as to put the tendo achillis on tension. Such an apparently minor symptom generally forebodes the appearance in months or several years of parkinsonism on that side of the body, even though the importance of the tremor in the early months is overshadowed by associated disturbances in the sleep rhythm, physical weakness, emotional instability, character changes and the like. Of particularly sinister omen during this period is a rapid loss of weight since it is frequently followed by the rapid development of the parkinsonian manifestations.

Given the above conditions, namely, an acute attack of epidemic encephalitis followed shortly by such symptoms, no diagnostic question can arise. It is quite a different situation in the absence of manifest evidence of the acute invasion of the central nervous system because many other pathological processes or constitutional disorders are capable of causing sleep disturbances, general weakness, neuroticism, slowness of psychomotor activity, tremor, etc. The clinical approach is also less certain in the given case, even with a more or less questionable history of acute encephalitis, when many years have elapsed between that attack and the appearance of recognizable parkinsonian symptoms and signs, a not infrequent experience. In the author's present series of cases there are

instances of comparative normalcy, physically and vocationally, over periods ranging from several years to thirteen years. After the process of identification and establishing the cause and effect relationship, a fine-tooth comb analysis of the interval period brings to light very interesting postencephalitic clinical material with the possibility of identifying not only incipient parkinsonian states but even preparkinsonian criteria.

**Preparkinsonian Fragments.**—1. *Abnormal Automatic Associated Movements.*—A significant preparkinsonian sign is the automatic flexion of one forearm in walking with a slow but steady ascent of the hand in front of the trunk, and not until the hand enters the lower limit of the patient's visual fields does he become aware of the fact. He will then consciously drop his hand but with a few more steps the hand again rises and remains poised in mid-air close to the trunk, much to the embarrassment of the individual. The involvement may be more limited in its segmentation when only the fifth finger becomes strongly abducted and rigidly extended. Other patients describe such an automatic movement occurring when engrossed in some such mental activity as reading; the individual suddenly finds himself distracted by an uncomfortable pressure in the lower abdomen caused by the hand slowly moving along his lap until the hand presses deeply into the abdominal wall. Or, the forefinger, of the hand resting on the paper while the individual writes, slowly rises in full extension without the person's knowledge until he starts a new line and then sees the extended forefinger. Occasionally both arms are involved and the hands slowly rise in front of the person until they reach the level of the chest. One young woman so affected attempted to overcome her embarrassment by raising her hands still higher intentionally as though she were adjusting her hat, and in this way she thought that passersby would not take especial notice of her raised hands.

2. *Hyperkinetic and Tonic Manifestations.*—Not infrequently the parkinsonian patient, in retrospect, will relate an early experience with his foot or hand which would either move slowly and rhythmically or go into a tonic spasm. For

instance, while sitting with knees crossed the foot of the crossed leg will start moving up and down in a rotary manner unbeknown to the patient until someone calls his attention to it. Another may find that the toes of one foot are continually pulling strongly up and down as his foot rests on the floor. Shifting of the feet alternately backward and forward sometimes is beyond the patient's control and he must get up from his seat lest he disturb others about him. The writing hand may grasp the pen so tightly as to make further writing impossible, and patients have referred to this as "grabbing the pen as though my life depended on it." It occurs with the steering wheel in hand and the individual is often embarrassed in traffic because of his inability to release his hold quickly enough to reach for the gear-shift handle; this symptom is nothing more than an example of perseveration. In the present series of cases there are three patients who had a slow rolling movement of the lower jaw for several years before the parkinsonian state was recognized. One woman came to look upon this symptom as a habit spasm and said that she had it for about ten years beginning shortly after her acute attack of sleeping sickness. A slow, rhythmical, ticlike movement of one corner of the mouth is reported by five patients in this group as having been the first indication of trouble.

3. *Oculogyric Crises and Blepharospasm*.—The diagnostic significance of tonic eye-rolling attacks is now unquestioned and one should not hesitate to identify such a symptom as encephalitic even in the face of negative past and present evidence. The attacks come on without warning, save in the minority where there is an aura of one form or another, and the patient suddenly finds himself unable to look straight ahead or continue reading because he cannot get his eyes down to the normal position. The oculogyration is generally upward and to one side, less frequently laterally deviated or downward. In the great majority of cases the attacks are tonic and remain deviated for minutes to hours. (A very rare form of attack is clonic spasm with the eyeballs moving sharply up and down.) The victim is unable to force the eyeballs down

and in desperation buries his head in a pillow and remains in bed until the attack subsides. Others can overcome the tonic spasm temporarily but only with great effort and then there is an associated clonic blepharospasm which ceases only when the eyeballs turn upward again. Great mental distress is experienced during the attack as well as numerous somatic dysesthesias and discomforts, particularly dizziness. Five patients of this group have committed suicide during an attack.

4. *Disorders of the Respiratory Mechanism.*—Hyperpnea in attacks occupies nearly the same position in the diagnostic scheme as the oculogyric crises. Should any physician observe a young, healthy-looking individual go through the characteristic cycle of a Cheyne-Stokes respiratory attack his first thought should be of the probable encephalitic background. These attacks recur at irregular intervals, and at the point of apnea the patient may lose consciousness momentarily and fall to the floor, or the facies become fixed as though the patient were having an attack of petit mal. Other respiratory attacks take the form of rapid breathing (hyperpnea) or very slow breathing (bradypnea). In other cases the respiratory rhythm may be very irregular and not follow any fixed rate or arrhythmia. Various bizarre movements of the trunk and upper extremities are utilized during the attacks in an attempt to overcome the discomfort by throwing into action the accessory muscles of respiration. Frequent sighing respirations may constitute the only respiratory disturbance or one may encounter various nasopharyngeal and palatal tics very much like habit spasm with sniffing, snorting, clearing the nose and throat or making laryngeal sounds from simple clearing of the throat to continuous moaning. Paroxysms of coughing occasionally disturb the encephalitic as well as changes in the quality of the voice such as suddenly breaking or an elevation in the tone with gradual weakening of the sound until the patient is unable to talk. These manifestations are also episodic and have their component of psychical overreaction.

5. *Postencephalitic Dyspituitarism.*—Between the acute attack of encephalitis and the later developing parkinsonian



state there occasionally occur disturbances in menstruation, fat metabolism and ectodermal alterations. Amenorrhea is quite a common aftermath and may persist for many months or years. It is associated with obesity and a rapid gain in weight of 50 or 60 pounds within a year. Hirsutism has been observed occasionally in these individuals with a change in the texture of the skin and the appearance of seborrhea facialis. The latter has been repeatedly pointed out as being a very common postencephalitic manifestation. Polyuria and polydipsia may be associated with the foregoing manifestations but are just as often present independent of them constituting the symptom-complex of diabetes insipidus. The pituitary gland is not the offending structure, the source is to be found in the neural connections of the pituitary in the interbrain. The central localization for these dysfunctions is further substantiated by the not infrequent finding of pupillary anomalies in these obese amenorrheic women, changes ranging from pupillary inequality and sluggishness of reaction to light to typical Argyll Robertson pupils.

6. *Miscellaneous*.—The preparkinsonian state is often unfathomable because of the vagueness of the subjective distress and the nonspecificity of the symptoms. But it is well to keep in mind the possible masked encephalitic background and search carefully for early signs of incipient parkinsonism the like of which will be described later. Chronic tiredness, loss of initiative, slight depression of mood, broken sleep, nervousness and shakiness of the hands when working under extra pressure and when excited, hypochondriacal tendencies, diurnal drowsiness, persistent aching in one limb, dizziness, loss of weight, a subjective sense or awareness of slowing of the thought processes are symptoms described by many chronic encephalitics before signs of parkinsonism become evident. Little wonder that these patients are subjected to thorough medical and surgical investigations and treatments for the purpose of removing all sources of infection purely on an empirical basis. Not uncommonly do we hear that one or another parkinsonian symptom or sign came on shortly after a minor surgical pro-

cedure such as tonsillectomy or the extraction of several teeth. Personality and character changes, especially frequent in children following acute epidemic encephalitis, may present a diagnostic problem in adult life and the nature of the change is recognized only in the light of a history of an acute attack of encephalitis or in the presence of parkinsonian evidence. Finally, it may be well to call attention to an interesting sign in young adults in the form of involuntary opening of the mouth which the patient can overcome but only momentarily. It is often present with the full-blown picture of paralysis agitans (encephalitic) but occasionally is an early sign long before the parkinsonian picture becomes typical.

**Objective Diagnostics.**—For absolute identification of any or all of the above described clinical material it is essential to recognize one or more early parkinsonian physical signs by a careful scrutiny of the appearance of the individual for changes in the facies, posture, attitudes, automatic associated movements, muscle tone as well as hyperkinetic unrest and evidence of neurovegetative dystonia. The facial changes include a seldom changing expression often referred to as fixed or blank, paucity of facial movements in talking and in emotional expression, a lessened frequency of the blink, and hypoactivity of one corner of the mouth in talking which may not be present when the patient voluntarily retracts the corners of the mouth (this may be reversed, *i. e.*, greater innervation in smiling than in voluntarily retracting the corners of the mouth, the so-called "dissociation of volitional and mimic innervation"). The posture and attitudes are characteristic and refer to any unusual manner, generally awkward, in which the patient holds his head, trunk and upper extremities. The elbows are more flexed than normal and the hands are held more to the front of the thighs than to their sides. The relative position of the fingers and thumb to one another as well as in relation to the palm is a very important feature of the early diagnostic criteria and will be discussed in a separate paragraph. The automatic associated movements are deficient in that the arms do not swing in association with the contralateral

lower limb when walking, the general motor behavior of the individual is slow and awkward not only in walking but in sitting down and arising from a chair. Frequently a limb remains poised in an awkward position either resting on a fixed object or just above the same. In turning toward the direction of a sudden auditory or visual stimulus the patient will turn his eyes more quickly than he will his head which is another evidence of dissociation in the automatic associated movements. This analysis of the motor functions, voluntary and automatic, can be carried on to apply to every act the human being is capable of performing.

A very helpful sign is the cogwheel motor phenomenon more often elicited in the biceps muscle. The examiner grasps the patient's arm in such a manner as to palpate lightly the belly of the biceps muscle while with the other hand the patient's forearm is alternately flexed and extended with variable speed at which time an irregular or broken relaxation of the biceps muscle is felt, a sensation akin to a clogged wheel rumbling over a plane surface. At the same time one will observe that the biceps muscle is overtoned as compared to the normal, hence the term "cogwheel motor rigidity." The phenomenon may be elicited in other muscles, particularly the triceps and forearm muscles, the latter by alternately flexing and extending the wrist. This is a sign of extrapyramidal disease of which paralysis agitans is an example. By hyperkinetic unrest is meant the presence of tremors of any kind and in any part of the body ranging from extremely localized fascicular or fibrillary tremors to coarse jactitations of an entire extremity. One should not expect to meet only with the so-called "typical pill-rolling tremor" in the encephalitic form of parkinsonism, because it is not the rule although it occasionally occurs. In the early stages the tremor may not be constant and be observed only when the patient holds his hands extended in front. A tremor may not be present when the limbs are at rest but brought out only with action, the intention tremor. It is quite characteristic, however, for the paralysis agitans tremor to continue with the limb at rest and cease entirely during the

performance of an intended act. In this portion of the survey we also include fluttering of the eyelids, localized tics, particularly slow, rhythmical twitching movements as of the neck with low amplitude of excursion indicating an incipient torticollis. Contrary to the characteristic loss of swinging movements of the arms in walking, occasionally one may observe an overactive and bizarre associated movement of one arm while the patient walks. Other involuntary movements occur very early in some instances such as tasting movements of the lips even with smacking sounds, movements of chewing, overaction of the tongue while talking so as to produce lisping or even mutilated articulation by the tongue constantly "trying to get out" through the oral orifice. The author has reported a very unique manifestation in the form of a rhythmical ticlike upward movement of the auricle due to involvement of an extra-aural muscle, and another case with a rotary movement of the auricle from involvement of the intrinsic muscles of the ear. Were it not for the presence of certain tonal signs in the hands the encephalitic nature of the tic would not have been considered. Quite a number of other kinetic manifestations may be observed which have more or less diagnostic significance to the individual clinician according to his personal experiences.

The term "neurovegetative dystonia" is used to include symptoms and signs referable to the autonomic nervous system such as the degree of pupillary dilatation or contraction, hypersalivation, bradycardia, tachycardia, motor and secretory dysfunction of the gastro-intestinal tract as indicated by the symptomatic expression and confirmed by roentgenological evidence; the dysfunction includes hypo- and hypersecretion and the same with motor innervation, the colon being affected either with a state of spastic colitis through all degrees of motor dysfunction up to an occasional instance of megalocolon, there being a number of reported cases in the literature of post-encephalitic Hirschsprung's disease. The examination should not fail to include the convergence power of the eyes because the most commonly observed postencephalitic ocular residuum is loss of ocular convergence.

**Diagnostic Triad for the Early Recognition of Incipient Parkinsonism.**—The author's triad (Arch. Neurol. and Psychiat., vol. 22, p. 709, 1929) is based upon the finding of asymmetry in the posture of the hands, in the manner of spacing the extended fingers and in the manner of performing rapidly repeated movements of touching forefinger to thumb. In the first sign one will note an increased flexion of the interphalangeal joints of one hand so that the thumb and forefinger are brought into apposition while in the opposite hand the fingers and thumb have a normal appearance of relaxation when the hands hang by the sides. The change may also consist of hyperflexion at the metacarpophalangeal joints with extension at the interphalangeal joints which still brings the thumb and forefinger together. For the second test the patient extends his upper extremities forward with the fingers separated and it is observed that on the affected side the thumb is not abducted as much as in the less involved extremity and the other fingers are irregularly spaced or closer together than in the opposite hand. During this test one will observe that there is a tendency for the extended position of the fingers to become exhausted with a gradual sinking of the fingertips to a lower level, and this might also apply to the wrist. The elbow of that limb will be seen to be less fully extended and even the hand incompletely pronated as compared to the other limb. In the third test the patient has his closed hands before his face and then attempts to rapidly and repeatedly bring the tips of his forefinger and thumb together when it will be seen that in the affected limb the height of the excursion is less than in the other hand, that the movement is less eumetric and is liable to become exhausted until it gradually stops while the other hand continues the normal movements. These signs merely indicate the existence of an early increase of muscle tone in the one limb. Although the triad may be positive in both limbs, it is true that the disease will manifest itself in its earliest stage by a greater development on one side than the other. This triad has been frequently elicited in persons who have not the slightest appearance of a parkinsonian on cursory

inspection. A positive triad may exist before the affected limb stops swinging in association with the contralateral lower limb in walking. An unequivocal incipient parkinsonian complex is constituted by the grouping of a positive unilateral triad with a suggestion of the cogwheel motor phenomenon in the arm, a suggestion of hypoactivity of the corner of the mouth on the same side either for emotional or voluntary innervation, and paralysis of convergence. This combination of physical signs has often been recognized in persons unsuspected of having parkinsonism, and on the strength of these findings the future disability of the patient was predicated only too truly because of the present impotence of our therapeutic armamentarium.

**Treatment.**—It is only fair to say at the start that there is no specific therapy for chronic epidemic encephalitis including parkinsonism. The virus causing acute epidemic encephalitis has not as yet been identified and no vaccine or serum has been produced which will effectively give or induce passive or active immunity. The consideration of immunological principles may not be as applicable to the chronic forms of the disease as to the acute because in our present state of knowledge it has not been definitely established that the parkinsonian harbors the active virus as does the acute encephalitic patient. Even the future discovery of a specific viricidal substance may not cure parkinsonism in the advanced stages because the degenerated brain tissue could not regenerate. Hope would be held out for those in the early stages of the disease and for this reason it behooves physicians to recognize the clinical manifestations in their incipient forms.

Nonspecific immunological attacks have been made on the disease with very little success, the methods ranging from intramuscular injections of milk to artificial hyperpyrexia through the use of physical or biological measures including malarial therapy. In the author's experience the strenuous fever therapy has done more harm than good to the parkinsonian. It would serve no purpose to enumerate the great number of foreign protein substances used because of the uniform lack of success in the therapeutic results. Many chem-

icals have been used intravenously but without convincing results. Von Economo, "father" of the disease, insisted in his late monograph on the use of iodine intravenously in heroic doses, 100 cc. of Pregl's iodine intravenously daily. In addition to iodine therapy he produced artificial fever with the injection of a material he called vaccineurin, a nonspecific protein. Von Economo introduced this treatment for the acute disease but suggested that all patients in the chronic stages be given the same treatment providing he had not received it previously during the acute attack. No such enthusiasm is expressed in this country over this treatment for obvious reasons.

The treatment of parkinsonism thus becomes limited to palliation of symptoms which is, fortunately, fairly satisfactorily accomplished by physiotherapy and certain medicaments. Knowing that parkinsonism is an incurable disorder and that the patient at best can expect only a stay in the progress of the disease, no effort should be spared, all conditions being equal, in instituting a strict hygienic regime for the purpose of conserving mental and physical energy. The parkinsonian has reached a point in life where he must balance his mental and physical budget if he would have the best of his remaining years. This applies to regularity in habits and moderation in all activities, physical, emotional and intellectual. The daily warm bath for thirty minutes followed by ten minutes of underwater passive and active exercise of his extremities is the most valuable form of physiotherapy. General massage does much for the physical comfort of the patient and his sense of well-being, but it must be given regularly and by a conscientious operator who is capable of differentiating between medical massage and a rubdown. A difficult but essential part of the program is reeducational postural and associated motor training which utilizes conscious direction of these motor behavior patterns in lieu of the lost automatic control. There are a number of these motor reeducational exercises and it is beyond the scope of this paper to elaborate thereon.

Greatest reliability is placed on derivatives of the solan-

aceous group, namely, hyoscine (scopolamine), atropine, and stramonium. Their effect is to depress the excitability of the parasympathetic nervous system with resultant lowering of the muscle tone which gives the patient a relaxed feeling and a sense of motor freedom. It is well to alternate these drugs so that the patient does not develop too great a tolerance to any particular one. Hyoscine hydrobromide is given in  $\frac{1}{16}$ -grain doses three times a day at the beginning with gradual increase up to  $\frac{1}{8}$  grain according to the individual patient's tolerance. Where there is much tremor or other forms of nervous unrest it is of advantage to combine the hyoscine with phenobarbital,  $\frac{1}{8}$  or  $\frac{1}{4}$  grain three times a day. When no further improvement takes place or when hyoscine fails "to hold" the patient, stramonium may then be more effectual. The latter is used in the form of fresh tincture or a soft pill made from the fresh leaves, or the extract of stramonium in doses equivalent to 25 minims of the fresh tincture to start with and gradually increasing the dosage up to the equivalent of 90 minims per dose three times a day. Atropine sulphate is exhibited in a dilution wherein 1 minim contains  $\frac{1}{500}$  grain. In this manner the dosage can be increased by 1 drop and gradually worked up with the increasing tolerance of the individual until he receives even as much as  $\frac{1}{10}$  grain in occasional cases. No two parkinsonians will react similarly to the various drugs, and it cannot be said that one or the other of this group is more beneficial for tremor or hypertonicity than the other, it is merely a matter of the personal equation. The remainder of the drug therapy resolves itself around symptomatic prescribing for the relief of the many and varied complaints of subjective distress.

Tantamount to most of the treatment of parkinsonism is psychotherapy which is to be used in conjunction with everything available be it physiotherapy, artificial fever or drug therapy. These patients are highly suggestible, tend to become hypochondriacal through morbid introspection, they are frequently depressed and develop persecutory trends and a number terminate their suffering by their own hand. A cure



should never be promised a parkinsonian but hope should not be destroyed. A generally acceptable dictum is—"Although cure cannot be promised, you may expect and hope for an arrest in the progress of your disease after which time we will see what can be done by reeducation."

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THE TREATMENT OF HERPES ZOSTER

IN common with other virus diseases, a specific treatment for herpes zoster is not available and one is forced to choose from a rather wide variety of therapeutic measures, many of them commended on the basis of experience with a few cases, few of them compared as to effectiveness with the results in control series, and none of them always successful. It seems timely, therefore, to consider the various methods of treatment suggested and to attempt a critical evaluation of each in an effort to outline a régime based on the best available information.

A short résumé of the principal features and variations in the course of herpes zoster will, we believe, emphasize the difficulty of an adequate analysis of the effectiveness of treatment. We may define zoster as a disease usually due to an unknown virus, occurring *sui generis* or during the course of a wide variety of other diseases, in which there are seen on the skin tense grouped vesicles on a highly inflammatory base, in the area innervated by one or more spinal ganglia or the homologous ganglia of the head, usually on the same side of the body. The vesicles may vary somewhat in size and the degree of inflammation may diverge widely, from a moderate erythema persisting for but a few days, to a destructive local gangrene. The more severe local reactions are noted particularly

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in aged debilitated individuals, and the prognosis in this regard must be guarded in such patients. An adenopathy of the adjacent lymph nodes is almost invariably found and this has been emphasized as a differential criterion from herpes simplex.

In a discussion of the treatment of zoster one must be mindful of the wide variation in the sequelae, dependent in part upon the structures innervated by the affected ganglia, and of the unpredictable, almost quixotic nature of the subjective symptoms noted. The pain and discomfort are often not at all proportional to the severity of the local manifestations. The following are the special regional forms of zoster most frequently offering difficulty in diagnosis and sometimes productive of unusual and severe sequelae.

*Zoster Ophthalmicus*.—In this type there is noted first an edema and swelling of the lids, with conjunctivitis and keratitis. Headache is common, and pain is more frequently encountered and often more severe than in thoracolumbar zoster. Aside from the immediate local changes in the eye (consisting of disturbances in the lacrimal secretion, appearance of vesicles on the cornea, and interstitial keratitis with or without ulcers), iritis may develop, and subsequent glaucoma has been described. Disturbances of the ocular innervation, which may sometimes be permanent, are seen in about 12 per cent of the cases.<sup>1</sup> Typical herpetic lesions are usually seen elsewhere in the region and the diagnosis must ordinarily rest on this finding.

*Zoster Oticus*.—The most significant contribution to a clarification of this at times puzzling syndrome was made a quarter century ago by Hunt.<sup>2</sup> He divided zoster about the ear into several types, in one of which the geniculate ganglion alone is involved, and the others in which mixed involvement of the facial, the acoustic, the auricular branch of the vagus, and the second and third cervical nerves occurs. Hayman<sup>3</sup> states that zoster oticus constitutes 28 per cent of all zoster about the head. We have recently observed a patient which illustrates the difficulty of early diagnosis in such cases. A woman, forty-five years old, had had a dermatitis of the left

external auditory canal for years. When first seen in the otolaryngology department of the University Hospital, she presented an erythematous swelling of the ear and preauricular region. She complained of headache (an almost constant finding in cephalic zoster) and some pain in the affected area. The morphologic appearance suggested erysipelas strongly but there was no fever. The left anterior cervical lymph nodes were enlarged. A provisional diagnosis of cellulitis was made, but with the appearance of the typical vesicles of herpes in the region anterior to the ear the true nature of the process became apparent. There had been no extension of the erythematous area and the vesicles, not discernible early in the process, became increasingly evident as the erythema subsided. There was no neuralgia, pain being frequently absent in herpes oticus, and under treatment with x-ray, salicylates, autohemotherapy, and calamine lotion, an excellent end-result was obtained.

Confusion of herpes zoster and simplex may occur, particularly when herpes simplex appears at unusual sites or is more extensive than that ordinarily seen. The rarity of recurrence in zoster and its frequency in simplex are, of course, well known. The most frequently encountered "unusual" sites of herpes simplex are the buttocks, particularly in women, and the genitalia in men. In many cases the differentiation of zoster from simplex cannot be made without resort to animal transfers in which, on scarification of the cornea of a rabbit with the contents of a herpes vesicle, a typical keratitis develops if the case is one of herpes simplex, while in zoster this reaction is not noted. Auto-inoculation is possible in herpes simplex.<sup>4</sup> In this connection the possible development of recurrent herpes simplex at the sites of inoculation must be kept in mind, especially since repeated inoculation has been suggested as a means of treatment.

Before proceeding to a discussion of the individual methods of treatment of herpes zoster we wish to emphasize several features of the course of the disease which have proved a source of difficulty in the interpretation of the specific effects of the various treatments in our series of 120 cases, and which

are, we believe, in part the reason for divergent opinions concerning the effects of treatment and for the frequently undue enthusiasm with which new types of therapy are introduced. The initial symptoms and sequelae of herpes zoster are in general directly proportional to the age of the patient. We have never seen a case of severe postherpetic neuralgia in a child under twelve in a fairly large clinical material at the Children's Hospital, and this impression of the relatively benign course of herpes in children is confirmed in the literature. On the contrary, zoster of relatively restricted extent in older individuals may be followed by neuralgia of a most persistent and exhausting character for months and even years after the attack. In young adults one often sees zoster of wide extent in which there is little complaint of pain and no interference with the patient's activities. In a case of bilateral herpes zoster observed by one of us (D. M. P.) in a man of thirty-seven, the patient stated that his subjective symptoms had consisted only of slight burning and tingling in the skin before and for two days after the appearance of the lesions. Obviously the results of any type of treatment in this case would have been rated as excellent as far as the neuralgic pain was concerned, whereas he had had no treatment.

It is apparent, therefore, that the probable symptomatic course in an individual case is often unpredictable except in children, and that only in relatively large series of cases including similar age groups, and with adequate control cases, can an accurate evaluation of therapy be made. The literature concerning the therapy of herpes zoster is in general distinguished by an absence of controls.

We shall consider in particular those measures with which we have had personal experience or concerning which a fairly adequate amount of data is available in the literature. These include (1) local measures, (2) drugs by mouth, (3) x-ray, (4) autohemotherapy, (5) pituitrin, (6) intravenous sodium iodide, (7) physiotherapy.

*Local Treatment.*—There seems to be no doubt that a cardinal principle in the treatment of zoster is to keep the

lesions dry. While there is ordinarily surprisingly little tendency to secondary infection, the opportunity for this is increased if wet dressing or poultices are employed. A simple calamine lotion is effective in most cases. The particular formula which we employ is as follows:

Calamine	
Zinc oxide	4
Phenol	
Glycerin	1
Rose water	
Lime water	ãã q.s. ad 120

In any but cases with superficial and relatively nondestructive lesions we believe it is preferable to omit the phenol, in spite of its local anesthetic effect. One half of 1 per cent each of menthol and camphor are a good substitute, except about the eye, where their use may produce marked lacrimation.

At times, particularly when there are lesions in intertriginous regions, a dusting powder may be useful. The following is suggested:

Camphor (pulv.)	0.6
Zinc oxide	
Boric acid (pulv.)	3.0
Talc	50.0

Local anesthetics are generally rather disappointing in their effect and have the disadvantage of retarding healing if any marked ulceration has occurred. If one is desired, anesthesin is useful, and may be incorporated in the above dusting powder in a strength of 1 to 5 per cent or in equal parts of lanolin and petrolatum. Nupercaine ointment (1 per cent) has seemed quite effective in some cases, and should be applied in small amounts thoroughly rubbed into the skin.

Occasionally the lesions become markedly pustular, and true secondary infection may also occur. Freshly prepared 1:4000 solution of potassium permanganate compresses, applied one-half hour three times a day, are useful. This may be followed by the application of a 2 per cent solution of gentian violet, or an ointment containing equal parts of the official ammoniated mercury, boric acid, and zinc oxide oint-

ments. The ointment should not be applied thickly, since this has the effect of allowing undue accumulation of exudate, and in some cases seems to retard healing.

Fox<sup>6</sup> has reported a method of applying an occlusive dressing with paraffin, in which he noted good symptomatic relief during the eruptive stage. A paraffin having a melting point of 114° to 117° F. was sprayed on the affected skin and covered with cotton held in place by bandaging. Fox recommends applying the paraffin daily, with careful gentle removal of paraffin remaining from previous applications. He noted no effect on postherpetic neuralgia.

*Therapy by Mouth.*—It is our custom to prescribe salicylates unless the process is very limited in extent or symptomless. Ten grains of sodium salicylate three or four times daily in adults has been the dosage employed. The barbiturates are useful for sedative and analgesic effect. We have discontinued the use of compounds containing amidopyrine. We have the feeling that morphine and its derivatives are employed much more extensively than is necessary, and the danger of inducing morphine habituation in prolonged postherpetic neuralgia must be considered.

In cases with ophthalmic involvement, consultation is advised. Fry<sup>6</sup> suggests the instillation of a 1 per cent atropine solution routinely three or four times daily, the use of 1 per cent holocaine solution if pain is present, and bandaging of the eyes if corneal ulceration occurs.

*x-Ray.*—This method of treatment has in our experience at times been quite striking in its effect on the local lesions but has frequently been disappointing in abating the neuralgic pain. Among the first to report an extensive experience with the method was Vignal<sup>7</sup> who believed that its value lay in the specific effect on the resorption of a round cell infiltrate of the spinal ganglia and posterior spinal roots. He stated that the pain may be increased after the first or second treatment but that improvement is ordinarily noted after the third irradiation. He recommends the employment of diathermy along with the x-ray.

The largest series of cases treated by this method which has come to our attention has been reported by Keichline.<sup>8</sup> He irradiated both the affected skin and the corresponding spinal ganglion in 62 cases. The factors which he employed were as follows: 148 r, 3 mm. Al, 30 cm. distance (K.V. not given). He found that in 90 per cent of his cases only one dose was required, while 8 per cent were given a similar dose the following day. In 2 per cent of his cases three doses, given at ten-day intervals, were required.

Pendergrass<sup>9</sup> has kindly given us his opinion of the value of and his method of administering x-ray in these cases. He has noted a variable effect, "some cases responding well while others do not." When the eruption is present he has employed the following factors: 135 K.V., 1 mm. Al, 30 cm. distance, 150 r, repeating this dose daily for a maximum of four times. For treatment of the ganglia and roots after the eruptive stage he has used the following: 200 K.V., 50 cm. distance, 0.5 mm. Cu, 50 to 200 r daily, for four or five applications.

We have treated 50 of our cases of herpes zoster by x-ray. We employed it particularly in cases showing severe local lesions or having appreciable neuralgic pain. The factors employed were 100 K.V., 30 cm. distance, no filter, 65 r daily to every third day for four or five doses. We have been impressed with the effectiveness of this measure in reducing the inflammatory reaction at the site of the lesions but have noted no very striking response of the pain. It is probable, of course, that very little effect on the spinal ganglia could be expected with this type of superficial therapy.

*Autohemotherapy.*—This method of treatment is widely employed in a variety of dermatologic conditions, of which zoster is one. Its use in general is almost entirely empiric and the theories concerning its mode of action are exceedingly tenuous and lacking in proof. We have employed it in 30 cases, frequently in conjunction with x-ray therapy. In one case there was a striking response which seemed definitely attributable to this factor in the treatment. The method was favorably reported on by several observers at the Nancy



meeting of French dermatologists in 1923,<sup>10</sup> and Beeson<sup>11</sup> has reported a series of 7 cases treated solely by this means. None of his cases had postherpetic neuralgia and the response of the local lesions was good.

Aside from its theoretical action, probably in effect similar to that of a foreign protein, it cannot be denied that autohemotherapy has a psychic value, especially when the procedure is performed in a not too casual manner. In view of the increasing importance of the psyche in many dermatologic conditions, including warts, the possible value of such an effect should not be lost sight of. Autohemotherapy is an almost completely innocuous procedure, when properly performed, and while its value in herpes zoster can hardly have been said to have been demonstrated adequately, further study of it seems worthwhile and its retention as a harmless ritualistic procedure seems defensible.

*Pituitrin.*—Following the introduction of this method of treatment in America by Sidlick,<sup>12</sup> in whose report is quoted the European experience of Vandel,<sup>13</sup> several other well considered and extensive reports concerning it have appeared. In four of Sidlick's cases the relief from pain was so prompt following the injection of pituitrin as to hardly admit of any objection to the argument that this treatment was the causative factor. Niles<sup>14</sup> reports 16 cases treated with pituitrin, in which 11 were well in an average of eight and one-half days. Niles included a control series treated in other ways, in which the results seemed less satisfactory in the cases in which the end-result was known. He saw no difference in the effect of surgical and obstetrical pituitrin.

Somers and Pouppirt<sup>15</sup> report their experience with pituitrin in 22 cases and offer an interesting theoretical consideration of its action. They make a distinction between two types of pain noted in zoster, the first type being of a sharp, stabbing, shooting character and of unlocalized distribution, the second being localized and of a burning, itching, shooting nature. They state that cases having the first type of pain most frequently suffer from prolonged neuralgia. The pain in

all their cases was of the second type and was relieved within six hours by pituitrin. They believe that the pain of zoster is the result of irritation of the sensory nerve endings by local vasodilatation and that the use of a vasoconstrictor such as pituitrin is reasonable on this basis. We have employed the extract in 7 cases and in at least 2 of these the relief from pain within a few hours after injection was striking.

Sidlick administered obstetrical pituitrin intramuscularly in doses varying from 0.5 to 1 cc. Somers and Pouppirt gave surgical pituitrin subcutaneously, starting with a dose of 0.2 cc. and increasing by 0.1 cc. increments up to 1 cc., at intervals of one to two hours. The larger doses were given only to young adults.

It is obvious that certain definite precautions must be observed in the administration of the extract. Pregnancy is, of course, an absolute contraindication, though Somers and Pouppirt state that pitressin may be used. In any occlusive vascular disease, particularly when the coronary arteries are involved, and in hypertension, we do not believe its use justifiable. Increased intracranial pressure is a contraindication. Patients must be warned of the probable effect of markedly increased peristalsis and the use of the extract in patients with any severe grade of constipation must, we believe, be guarded. Sidlick noted faintness in some of his cases.

From our own and the reported experience of others, we believe pituitrin is of definite value in many cases. One of its advantages is that the probable effectiveness of the method in an individual case can usually be determined within three or four days.

*Sodium Iodide.*—Ruggles<sup>10</sup> has reported 15 cases of zoster treated with gratifying results by intravenous sodium iodide. His method consisted in the administration of 20 cc. of a 10 per cent solution on the first, second, fourth and seventh days. We have used this treatment in 15 cases, in all but 2 of which either autohemotherapy or x-ray were also used. In one case treated with sodium iodide alone the local response was prompt. The patient was a boy of nine in whom the eruption was orig-

the concomitant administration of 10 cc. of the patient's own whole blood intramuscularly is suggested.

3. If pituitrin is contraindicated or ineffective the administration of 10 cc. of a sterile 10 per cent solution of sodium iodide on successive days is suggested, preferably combined with

4. x-Ray therapy: (a) 75 to 150 r, 100 to 135 K.V., 30 cm. distance, without filter or with 1 to 3 mm. Al every one to three days to the skin lesions; (b) 50 to 200 r, 200 K.V., 50 cm. distance, 0.5 mm. Cu filter daily for four or five days over the affected ganglia.

5. General ultraviolet light in suberythema doses, protecting the areas exposed to x-ray, or better, natural sunlight, or dry heat.

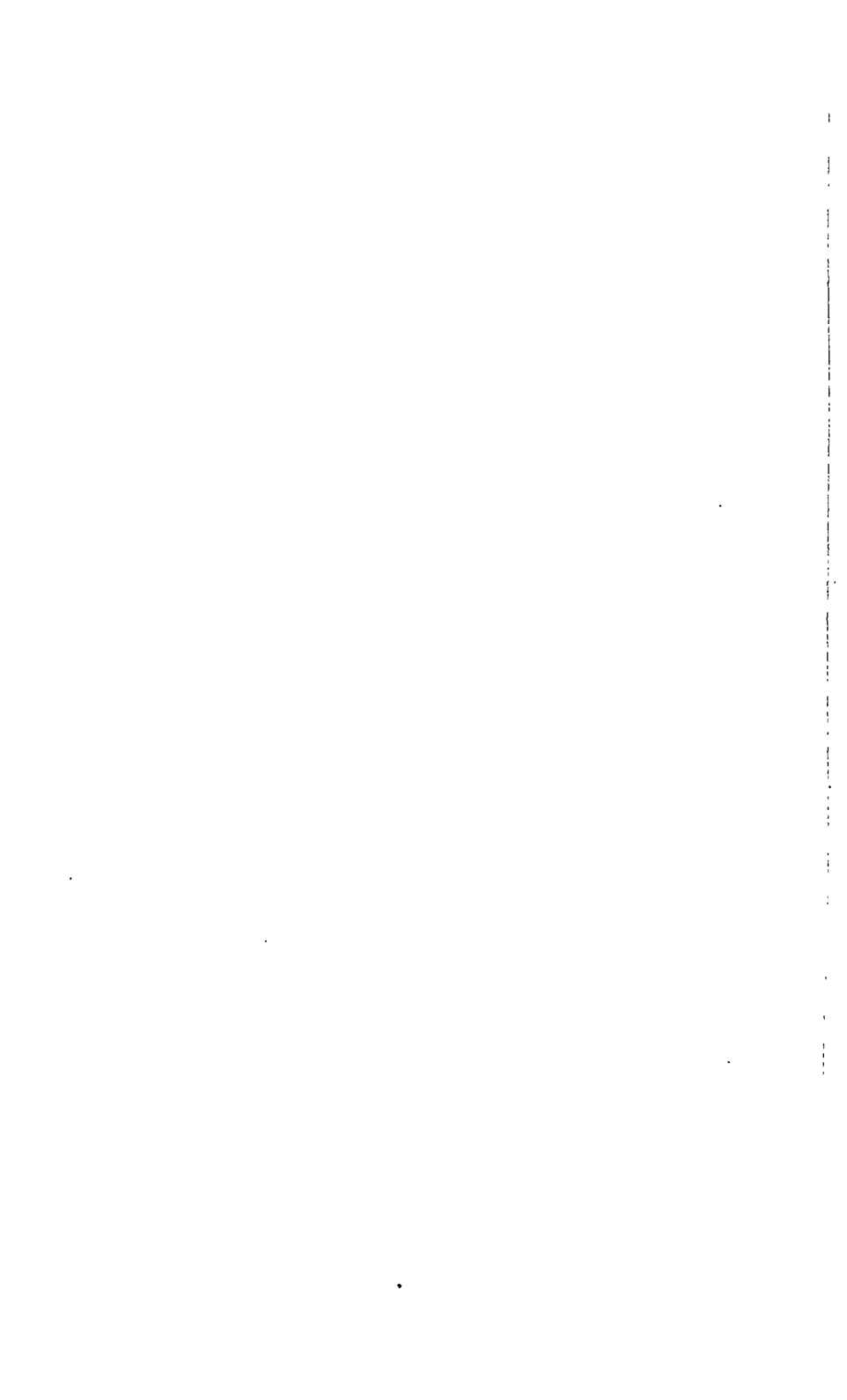
6. Diathermy over the region of the affected ganglia.

7. Neoarsphenamine in tonic doses (0.3 to 0.45 Gm.) at four-day intervals for four doses, being certain that the patient does not have obvious organic syphilis and observing the rule of taking a "baseline" Wassermann.

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## CLINIC OF DR. THOMAS FITZ-HUGH, JR.

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### GENETIC ASPECTS OF CERTAIN BLOOD-SYSTEM DISORDERS

DESPITE the danger to the student of hematology of listening too sympathetically to the siren song of "constitution pathology" with its seemingly easy answer to some unsolved problems of etiology, and despite the great complexities of genetic science (even as applied to *Drosophila*, not to mention *homo sapiens*) it seems nonetheless worth while to review the now accumulated data of clinical hematology from a genetic standpoint—with due apologies for the presumption.

The following list (Table 1) of anomalies and diseases of hematologic interest begins with hemophilia which has been called "the most hereditary of all hereditary disorders" and

TABLE I

- I. Blood-system disorders known to have a genetic basis.
  1. Hemophilia.<sup>1</sup> 2. Hereditary hemorrhagic telangiectasis.<sup>2</sup> 3. Hereditary hemorrhagic thrombasthenia.<sup>3</sup> 4. Hemolytic ictero-anemia.<sup>4</sup>
  5. Sickle-cell trait.<sup>5</sup> 6. Ovalocytosis.<sup>6</sup> 7. Pelger's familial anomaly of nuclei.<sup>7</sup>
- II. Blood-system disorders believed by some authorities to have a genetic basis.
  1. Pernicious anemia.<sup>8</sup> 2. Idiopathic hypochromic anemia and chlorosis.<sup>9</sup>
  3. Erythroblastosis of infancy.<sup>10</sup> 4. Familial polycythemia.<sup>11</sup> 5. Gaucher's<sup>12</sup> and Niemann-Pick's<sup>13</sup> diseases.
- III. Blood-system disorders which may possibly have a genetic basis.
 

<ol style="list-style-type: none"> <li>1. The leukoses<sup>14</sup></li> <li>2. Lymphosarcoma<sup>15</sup></li> <li>3. Leukosarcoma<sup>15</sup></li> <li>4. Hodgkin's disease<sup>15</sup></li> </ol>	}	Malignancy?	<ol style="list-style-type: none"> <li>5. Purpura hemorrhagica<sup>16</sup></li> <li>6. Agranulocytic angina<sup>17</sup></li> <li>7. Favism<sup>18</sup></li> <li>9. Familial eosinophilia<sup>19</sup></li> </ol>	}	Allergic constitution?
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ends with certain questionably classified entities whose chief claim to genetic consideration rests largely upon that uncertain hypothesis called the "allergic constitution"—which is probably partly genetic and partly the result of acquired intra-uterine transfer of sensitization.

Before entering upon a discussion of these conditions I would like to remind you of a few clinically important findings and deductions of genetic science. I am indebted chiefly to

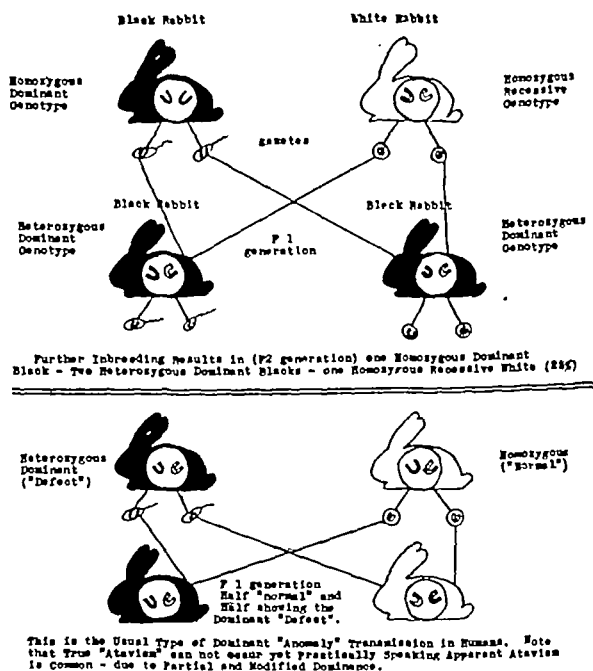


Fig. 8.

Professor Mohr's admirable book<sup>20</sup> for the next two diagrams and their explanation.

In Fig. 8 I have attempted (after Mohr) to illustrate the simplest type of dominant and recessive unit character transmission employing respectively the conventional black and white rabbit symbols. If one wishes to work out the genetic possibilities of a certain dominant anomaly he may imagine that the black rabbit is the "anomalous" or "diseased" individual

and the white rabbit the "normal." If on the other hand a recessive anomaly is being considered the white rabbit becomes the diseased representative in a "normally" black population.

Since most human dominant anomalies are present in heterozygous form—very rarely in homozygous or "double dose" composition—it is obvious that the usual rule of dominant character transmission is: 50 per cent "affected" and 50 per cent "normal" offspring. When we find in the hereditary incidence of a given human anomaly an approximation

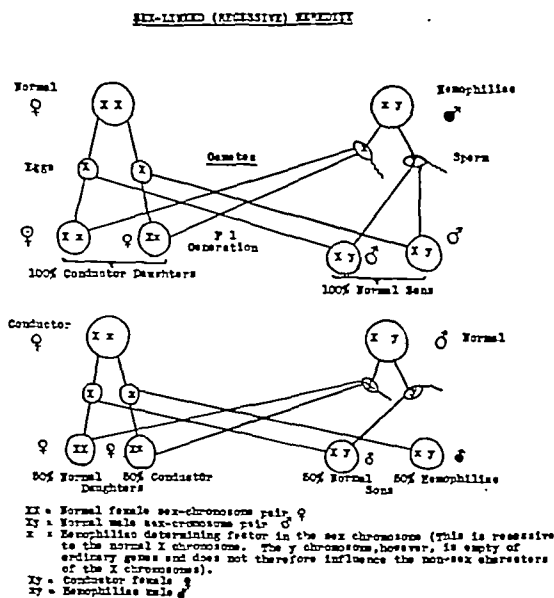


Fig. 9.

of this 50-50 ratio in each generation we are inclined to suspect a dominant gene factor. Despite the obvious logical fallacy of such a deduction, and despite the fact that there are other complex genetic modifications that may simulate this ratio it nonetheless appears to be a fairly sound inference if based on sufficiently accurate and numerous observations. On the other hand, dominant anomalies as observed in the clinic are rarely so striking and uniform as the "black rabbit symbol" would imply. There are modifying factors which may



make certain dominant anomalies mild and inconspicuous. Hence the apparent paradox that although dominant anomalies from a truly genetic standpoint do not skip generations (*i. e.*, exhibit no atavism) they nevertheless clinically sometimes appear to do so. This "paradox" is frequently encountered in the heredity of hemolytic ictero-anemia and hemorrhagic telangiectasia.

The genetics of hemophilia are illustrated (after Mohr) in Fig. 9. This is another type of mechanism—the so-called "sex-linked recessive pattern"—to which we shall refer again.

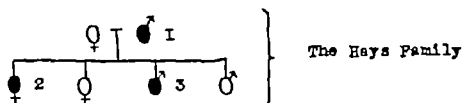
**Some Blood-system Disorders Conditioned by Dominant Genetic Anomalies.**—*Hemolytic ictero-anemia* of the Chauffard-Minkowski type is dependent in part at least upon the production of abnormally fragile and thick red cells<sup>21</sup> ("spherocytes"). It is exhibited by both sexes, transmitted by both sexes, and varies in its manifestations all the way from a symptomless "latent" anomaly to a crippling and even fatal disease. A practically "normal" or latent "carrier" may transmit it in severe form to offspring—among whom it may also vary greatly in severity. This is merely one of the unsolved mysteries which include also the characteristic relapsing and remitting course of the disorder in any given individual. These facts point not only to complex genetic factors but also to the subtle interplay of environmental factors as well. Despite these mysteries this disease offers a most satisfactory therapeutic opportunity. The results of splenectomy are dramatic and gratifying—even though the underlying genetic "defect" of course remains.

In the two family charts presented in Fig. 10 the parent responsible in each instance for the disease in the children was unaware of any real ill health. In the H. family, however, the father was found to have an enlarged spleen, increased fragility of the red cells and a reticulocyte count of 10 to 15 per cent and in the M. family the mother had slight icterus and a moderately increased fragility. It might have been scientifically instructive (but probably humanly tragic) if "fate" had brought these two apparently normal individuals

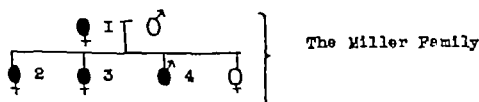
together as husband and wife. Genetic science is replete with evidence that "a dominant gene, which when heterozygous causes only trifling malformations, may in double dose or homozygous condition cause very serious or even lethal disturbances." \*

*Hereditary hemorrhagic telangiectasia* exhibits the same sort of hereditary incidence and the same inexplicable variability of manifestations as hemolytic ictero-anemia. Some years ago I called attention to the fact of apparent atavism<sup>22</sup> in this—a genetically dominant disorder which strictly speaking cannot be truly atavistic. The practical importance of

HEMOLYTIC ICTERO-ANEMIA - A DOMINANT MENDELIAN TRAIT.



All individuals in this chart personally examined except case 2 who died of anemia and jaundice. Case 3 splenectomized with excellent result. Case 1 - mild - refused splenectomy.



All individuals examined. Case 1 "latent". Case 2 - age three years 8 months, case 3 - age eleven years and case 4 - age nine years all severe and all splenectomized with excellent results.

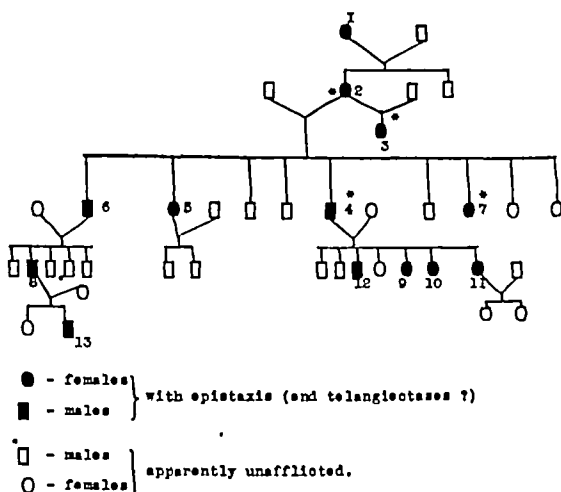
Fig. 10.

these "latent" or "mildly affected" carriers in the heredity of many dominant-gene anomalies cannot be overstated.

*Ovalocytosis* is, as far as is known, a harmless anomaly of human erythrocytes. It is I am sure more common than generally realized. My office technician has kept a record for the past few years of the occurrence in otherwise normal blood counts of patients showing 5 per cent or more of oval cells in the stained spreads. To be counted in these statistics the hemoglobin (Sahli scale) must be 80 per cent or better and the red cell count 4 million or better so as not to include "poikilocytosis." Our figures show a 6 per cent incidence of ovalocytosis in the last 600 normal-patient blood counts.

\* Mohr: Heredity and Disease, Published by W. W. Norton and Co., Inc.

That this anomaly is probably a dominant one is suggested by the absence of atavism in well-studied families and by the nearly 50 per cent incidence in the generations exhibiting the trait. I have studied the reticulocytes, fragility, gastric acidity and agglutinins (blood type) of affected and nonaffected members of two families exhibiting this anomaly without discovering any significant correlations. Here too, however, it would be interesting to observe the effect of this "harmless" hetero-



\* Known to have died of the disease, # 2,3,4,7

1. Patient's maternal grandmother. 2. Patient's mother (who married twice). 3. Patient's half-sister. 4. Patient Mr. M.G., 5, 6, 7 siblings of the patient. 8. Nephew of patient. 9, 10, 11, 12 Children of the patient. 13. Grand-nephew of patient.

Fig. 11.

zygous dominant in double dose or homozygous composition. Such unions must occur if ovalocytosis is as common as I think

The *sickle-cell* trait is another dominant-gene anomaly which, like hemolytic ictero-anemia, may vary in different individuals from a harmless laboratory entity to a fatal disease. Unlike hemolytic ictero-anemia, however, there is no "cure" nor even a useful remedy.

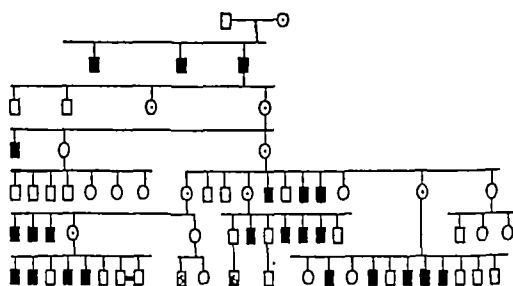
**Other Blood-system Disorders Known or Thought to be Genetically Conditioned.**—*Hemophilia* is a disease of males only. Although absolutely hereditary it is constantly

cropping up, especially in the United States among the first or second generations of native-born boys descended from Old World grandmothers and great-grandmothers without a discoverable trace of the pathognomonic "family history." When one looks at the genetic mechanism (Figs. 9 and 12) it is easy to see how through several predominantly feminine generations (without perchance bleeder boys to keep the memory alive) conductor females might carry on a hemophiliac strain from mother to daughter with a good chance of losing track of the tell-tale record. We have had three boys recently in the wards of the University Hospital with classical hemophilia but with absolutely "negative" family histories. The diagnosis in each instance was established not only clinically (by the record of hemorrhages from trivial trauma since infancy, hemarthroses, etc.) and hematologically (by the prolonged coagulation time of the blood, with normal platelet count, etc.) but also by that pathognomonic test of platelet function<sup>23</sup> which I believe is conclusive. If hemophilic blood is collected carefully and allowed to "sediment," the platelets can be removed in the plasma from above the "buffy coat." Such hemophilic platelets (washed in saline) when added to freshly shed hemophilic blood do not hasten the coagulation of this blood. If normal washed platelets, however, collected from above the "buffy coat" of normal citrated human blood, are added in equal quantity to freshly shed hemophilic blood the latter clots quickly and normally. Hence if we have a known hemophiliac to furnish the "test-object blood," an undiagnosed suspect's blood platelets may be added. If the suspect's platelets cause prompt clotting of the known hemophiliac's blood then the suspect is not a hemophiliac. If the suspect's platelets, however, do not cause the hemophilic blood to clot any sooner than it is shown to do at the time spontaneously there is thus adduced strong evidence in favor of the diagnosis of hemophilia in the suspect.

Hemophilia has thus far resisted all efforts at curative therapy. The ovarian gland and estrus hormone therapy of Birch<sup>24</sup> has failed completely in our hands. The placental

extract therapy of McKhann<sup>25</sup> and his associates has also not been of significant value in the 3 cases in which we have tried it.

Space does not permit of detailed discussion of the other diseases and anomalies listed at the beginning of this review. I have attempted in the bibliography to include some important "leads" to their genetic consideration. Pernicious anemia and so-called "idiopathic hypochromic anemia" appear to have a common basis in gastric deficiency and occur often enough in successive generations of families to warrant the suspicion



Pedigree, showing sex-linked mode of inheritance in hemophilia. Squares indicate males; circles, females; black symbols, persons afflicted with hemophilia; circles with dots inside, conductor females; clear symbols with numeral inside indicate a corresponding number of unaffected offspring; z means twins. Most of the hemophilic males died of hemorrhage at an early age. Note that transmission through the male in the second generation occurred. The male inherits hemophilia from his mother, however, never from his father.

Since conductor females cannot be differentiated from normals except by the test of reproduction it is obvious that in hemophilic families only the unaffected males can reproduce with impunity. (Adapted from Macklin (1)).

Fig. 12.

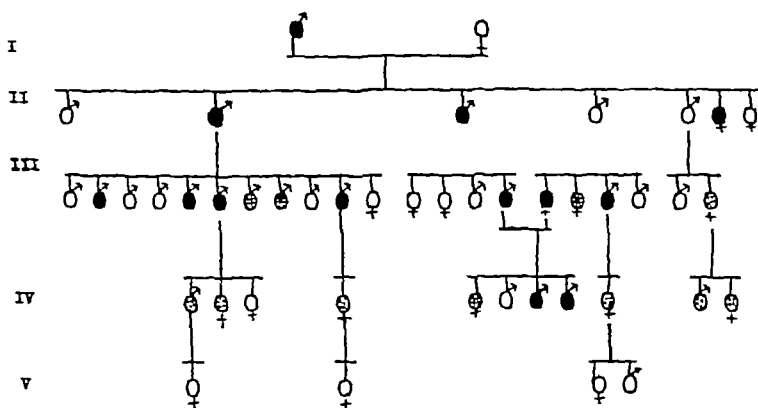
of a genetic predisposition. The pedigree (Fig. 13) taken from Heath's article<sup>26</sup> is a striking illustration of this point of view.

One must of course be critical of the assumption of a genetic factor if the assumption is made without due consideration of such factors as common family environment, contagion and common dietary deficiencies and excesses.

When one considers the malignancy-like members of the blood-system diseases from a genetic viewpoint there is very little convincing evidence to be seen. There are records, how-

ever, of familial leukemia, polycythemia, lymphosarcoma, etc. The analogies of human to mouse leukemia are striking; and the genetic factor may be championed just as well by those who believe in a virus cause as by those who adhere to the theories of a purely cellular mechanism of malignancy. For it has been shown that virus susceptibility has an important genetic basis.<sup>27</sup>

Concerning the "allergic constitution" and blood-system disorders that may possibly be related thereto one may merely speculate.



DESCRIPTION OF CHART. - ● Died of anemia. ⊙ Living, has pernicious anemia. ⊕ Living, has secondary anemia.

Fig. 13.

I have a growing conviction that many puzzling "blood pictures" may eventually be shown to result from hematopoietic participation in the biologic reactions of idiosyncrasy and allergy. This suspicion includes some of the purpuras and other hemorrhagic states, leukopenias, hypoplastic and aplastic anemias, thrombocytopenias, and granulocytopenias. My present concept<sup>17</sup> of the condition commonly called agranulocytic angina, which I have attempted to symbolize in Fig. 14, includes a complex liver-bone-marrow-blood-stream reaction on a sensitivity basis—which may or may not be genetically conditioned. Perhaps this is carrying the genetic viewpoint to a

THE SYNDROME OF PERNICIOUS LEUKOPENIA (AGRANULOCYTIC ANGINA)

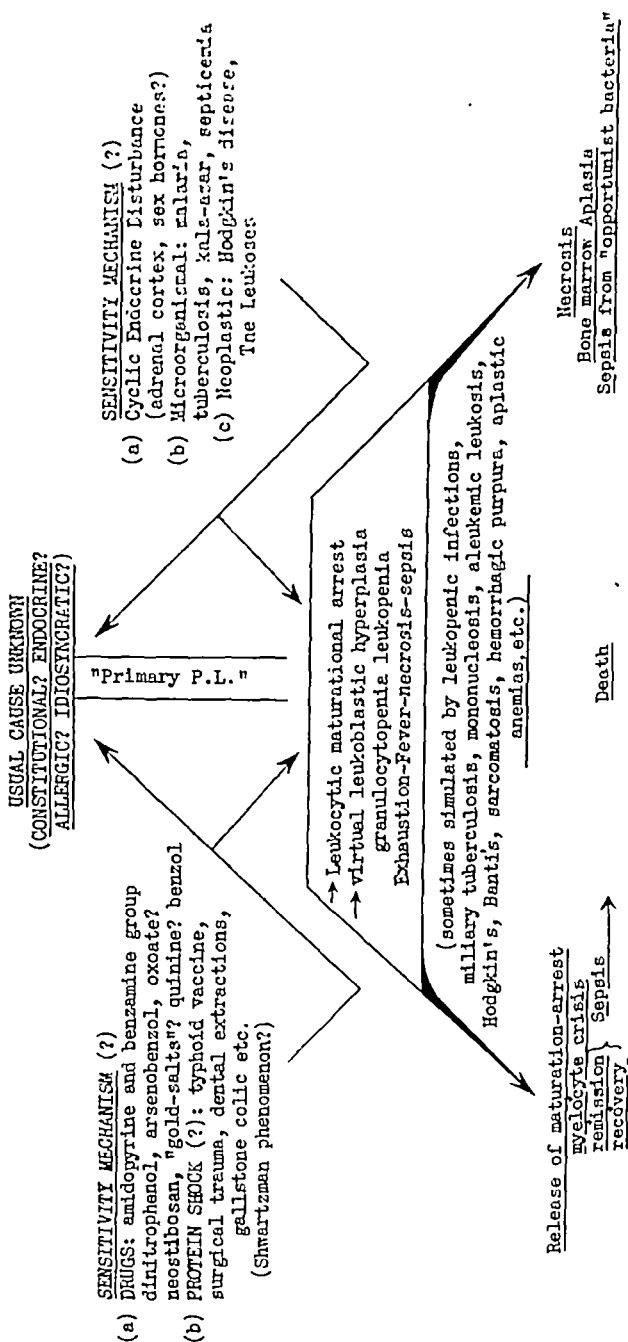


Fig. 14.

sort of clinical *reductio ad absurdum* but as long as a given disorder seems to present aspects of allergy it must be viewed as possibly genetically conditioned—in part at least.<sup>28</sup>

And finally, and again *perhaps*, this may be no more than an empty restatement of the truism that all biological reactions are, in part at least, genetically conditioned.

**Conclusions.**—1. An hereditary basis may properly be considered along with other factors in the etiology of many of the so-called “blood diseases.”

2. The mere absence of family history of a given disorder is no proof of its nongenetic basis. Clinical (*i. e.*, apparent) atavism even in dominant anomalies is not uncommon. Atavism is almost the rule in anomalies conditioned by recessive genes.

3. The supposition or proof of a genetic basis for a given disorder does not preclude helpful therapy to the afflicted individuals nor should it be viewed as necessarily detrimental to the proper scientific attitude of investigation of other etiologic factors.

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BOTULISM—A REPORT OF TWO SUSPECTED CASES

No greater emergency confronts the medical profession than an outbreak of botulism. The patient with signs and symptoms of this intoxication may have but remote prospects of recovery despite the best available treatment, but those treated with specific antitoxin before the onset of symptoms will recover.

Botulism (botulus—sausage) was first described in 1735<sup>1</sup> and was long attributed to meat, especially to sausage from Wurtemberg, a great packing center. In 1894 Van Ermenegem<sup>2</sup> isolated the spore-forming *Clostridium botulinum* from an infected ham, during an outbreak of the disease at Elezelles in which 3 of 20 patients died. This organism under anaerobic conditions was found to elaborate a virulent exotoxin, which produced typical symptoms of the disease in susceptible animals.

Outbreaks of botulism are not common. Only 6<sup>3-8</sup> are reported in Great Britain. In America 193 outbreaks (645 cases) have been recognized between 1899 and 1932 (Beckman),<sup>9</sup> more often in the West. Doubtless the majority of physicians have never seen such a patient. The 2 cases reported here were the first of the kind to be admitted to the Pennsylvania Hospital—the oldest hospital in the United States.

The general mortality rate is about 65 per cent,<sup>10</sup> and in some outbreaks, *e. g.*, the Loch Marie tragedy, it reaches 100 per cent. Successful treatment depends on the prompt-

ness of the diagnosis. These facts and the likelihood that one may be called upon to recognize the disorder and conduct treatment without notice warrant the report of every case, in this manner keeping the subject constantly before the profession.

The *Clostridium botulinum* is widely distributed in the soil, but there is no proof that the organism or its spores are themselves pathogenic: they produce the deadly toxin only under anaerobic conditions in suitable media (most preserved foods). This toxin and the bacilli are readily destroyed by boiling but a minimal temperature of 110° C. maintained for fifteen minutes is required to kill the spores. The works of Estey and Meyer,<sup>11</sup> Dickson,<sup>12</sup> Leighton,<sup>3</sup> and Lang<sup>13</sup> should be consulted for further details on this subject. Botulism can be prevented by adequate pressure-cooking of preserved food, or by destruction of the toxin through boiling immediately before ingestion. Preserved food with any evidence of decomposition, *i. e.*, unnatural color, odor, or swelling of the container, should be boiled or discarded.

Most of the commercial methods for preserving foods involve sufficient cooking to destroy both the bacillus and its spores, but home-preserved foods are not ordinarily subjected to a temperature adequate for this purpose. Any sealed food container—glass, tin, wood, paraffined gauze or even the visceral covering of sausages—maintains sufficiently anaerobic conditions to allow the bacillus to produce toxin. Home canned fruits and vegetables have been the common offenders in this country, while prepared meat is the usual source of the toxin in Europe. Oddly enough, the affected food may not be distasteful, though a mild rancidity is the rule. Foods preserved in liquids may be especially poisonous. The escape of some people who have eaten such food is attributed to the absence of the toxin in that portion which lies above the fluid level in the container.

It has been claimed that the organism can elaborate the toxin within the stagnant gastro-intestinal tract; this possibility would indicate active treatment against the constipation

present in most cases. The bacilli have been found in the stool eleven days after the ingestion of the contaminated food.<sup>14</sup> The toxin taken by mouth or introduced parenterally is highly poisonous, and is not destroyed by peptic or tryptic digestion. Alcohol is believed to have a detoxifying effect; cases have been reported in which it was taken with the poisoned food and apparently prevented fatalities.

Several strains of *Clostridium botulinum* have been identified; two ("A" and "B") are pathogenic to man. "A" toxin produces in chickens "limberneck" and death within twenty-four hours, while "B" toxin does not. The specificity of the antitoxin—unless polyvalent or mixed sera are used—makes recognition of the strain an important matter.

The cases reported below, though probably too advanced to be benefited by antitoxin when first seen, were not recognized as botulism until the postmortem examination excluded

TABLE I  
SYMPTOMATOLOGY

<i>Characteristic Symptoms and Signs of Botulism</i>	<i>Case I</i>	<i>Case II</i>
Weakness or fatigue	+	+
Dizziness	+	+
Diplopia	+	+
Dilated pupils	+	+
Loss of light reflex	+	+
Ptosis of the eyelids	+	+
Paralysis of speech	+	+
Paralysis of swallowing	+	+
Dryness of the mouth	+	+
Respiratory distress	+	+
Diminished reflexes	+	+
Restless	+	+
Mental alertness	+	+
Intact sensorium	+	+
Absence of fever	slight fever	+
Elevated pulse rate	+	+
Persistent constipation	+	+

*Table I.*—The subjective and objective manifestations of our two patients, compared with the characteristic symptoms of botulism.

the clinical diagnosis, *vide infra*. In retrospect, the clinical manifestations and autopsy findings are in accord with the diagnosis of botulism. We are indebted to Dr. Bernard Alpers for his neurological studies of each patient.

The contents of Table I emphasize the characteristic symptoms of botulism and the parallel likeness of our 2 cases, in which the outstanding symptoms were dizziness, diplopia, ptosis of the eyelids, paralysis of speech and swallowing and persistent constipation. The low or absent fever with an elevated pulse rate, the mental alertness and the intact sensorium with the rapidly progressing palsies were also striking.

Dickson<sup>15</sup> has concisely presented the clinical picture of botulism in the following words—"A sensation of weakness and fatigue, vertigo, uncertain gait, muscular weakness, blepharoptosis, mydriasis, loss of pupillary reflexes to light, diplopia, dryness of mouth, difficulty in talking and swallowing, persistent constipation, normal or subnormal temperature, with rapid pulse, intact skeletal reflexes and absence of mental or sensory dulness are all characteristic signs of botulism and together constitute a clinical picture, which, once seen, cannot be forgotten.

"The condition which is most closely resembled is belladonna poisoning.

"The onset of symptoms varies from a few hours to several days after the toxin is ingested—in a series of 200 cases a few within twelve hours, 74 per cent within forty-eight hours and all but 8 within four days."

**Case I.**—B. P., a sixteen-year-old Italian stenographer, was admitted to Dr. T. McCrae's service on January 5, 1934. The history was obtained in writing, as she was unable to talk. Her chief complaints included drooping of the eyelids, flashes of light before the eyes, dimness of vision, dryness of the mouth, difficulty in swallowing, and inability to use her tongue properly.

*Family History.*—One brother (Case II) was examined the same day because of vertigo, and another brother of three

years was ill at home with an acute respiratory infection. The patient's mother had had some stiffness and swelling of the neck with a sore throat and malaise on January 1st and 2nd. Eight siblings living in the same house were entirely well. A package of freshly gathered mushrooms was consumed on January 1st, chiefly by the father without ill effect, while several of the children, including both patients, had eaten small portions.

*Past Illnesses.*—Measles in early childhood, scarlet fever and diphtheria at five, acute tonsillitis at ten, and tonsillectomy at thirteen.

*Present Illness.*—The patient was intelligent and cooperative, and was well prior to this illness. On January 2nd, after eating a "wiener" at a lunch counter (10 A.M.) she had epigastric discomfort and was nauseated. Her eyes felt heavy, and by evening she could hardly keep them open, though she was not drowsy, and lights appeared extremely bright. Her vision was dimmed so that she was unable to read, but she could recognize people and distinguish colors.

Next morning (January 3rd), she had diplopia and her throat felt "stiff." Liquid foods regurgitated through her nose, and solid food stuck in her throat. On the morning of January 4th, she had a mild headache; her vision was greatly impaired and diplopia was marked; she could no longer identify colors or details; swallowing was extremely difficult, and she could neither articulate, clear her throat, nor cough effectively. Subjectively, her tongue seemed hard, shortened and stiff.

When admitted on January 5th, having had no previous medical attention, she complained of the following additional symptoms; inability to grip objects firmly, general sense of weakness and fatigue. She could walk only with support. Her appetite was good; she had been unable to eat for two days because of choking. Her bowels had not moved on the second and third days of her illness, but on the fourth day just before hospitalization, she had had a small, difficult movement—the only evacuation during her sickness. This stool was not available for the examinations suggested below.

*Physical Examination.*—(January 5th, 8 P. M.) Patient comfortable, nutrition and color good, cheeks flushed, skin dry, rectal temperature  $99.1^{\circ}$  F., and pulse rate 124. The marked ptosis of both upper lids gave her a lethargic appearance, though she was mentally alert and keenly aware that she was seriously ill. Her vision and speech were greatly impaired, her voice had a nasal tone, and she was unable to swallow or clear her throat. The eyelids could be closed firmly, but could not be elevated. The pupils were widely dilated; direct and crossed light reflexes were present but diminished; the eyes could not be externally rotated and there was slight reddening of the right optic disk. She was unable to wrinkle her forehead, and there was diminished retraction of the angles of the mouth upon deliberate effort to smile. She could not purse the lips, whistle, or open her mouth widely, though she could clench her teeth firmly. Protrusion of the tongue was limited, and she was unable to touch the angles of the mouth with the tip of the tongue. Mucus accumulated in the oropharynx as she could neither swallow nor expel it. The pharyngeal and palatine reflexes were absent. At this time the neck muscles were not weak, and shrugging of the shoulders was possible. The tendon reflexes were active. Both hand grips were definitely weakened. The heart, lungs and abdomen were normal to clinical examination.

At midday on January 6th, lateral deviation of the left eye occurred when a voluntary effort was made to depress it, and the masseter muscles had become definitely weakened. At 6.30 P. M., there was bilateral complete blepharoptosis; slight deviation of the left eye medially and of the right eye laterally; difficulty in depressing the right eye; limited upward movement of each orbit; inability to close the eyelids firmly but the corneal reflexes were active. There was further weakness of the facial muscles causing inability to smile, whistle, open the mouth or blow out the cheeks. The palate was immobile and the tongue could not be protruded. The hand clasps were weaker, as were the muscles of the extremities, while the biceps, triceps and Achilles reflexes were absent.

At 11.30 P. M., the patient became very restless, tossing the hands and feet about, and an hour later was incontinent of urine. The breathing became labored, cyanosis appeared, and at 1.05 A. M. (January 7th), respirations ceased abruptly; death occurred before a respirator could be utilized, approximately one hundred and eleven hours after the onset of symptoms. The pulse rate had increased steadily to 152 shortly before death, and the rectal temperatures had ranged between 99° and 100° F.

*Laboratory Data.*—Blood: leukocytes, 14,000; red blood corpuscles, 5,800,000; sugar 0.093 per cent; urea nitrogen, 0.016 per cent. Urinalysis: normal except for high specific gravity (1.036). Stool and gastric contents were not obtained. Lumbar puncture: pressure 7 mm. of mercury, Queckenstedt test negative, fluid slightly cloudy, cell count 4 (all lymphocytes), globulin 2 plus, sugar 0.079 per cent, Wassermann negative, colloidal gold curve normal, culture sterile, and there were no organisms found in stained smear. Cisternal puncture (postmortem): slightly cloudy fluid, globulin 2 plus, cell count 5 (all lymphocytes).

An autopsy was performed by Dr. A. Wallis and an exhaustive study of the central nervous system is being reported elsewhere.<sup>16</sup> In brief, pathological changes were found in the anterior horn cells of the spinal cord and in the neurons of the cranial motor nuclei. Also noteworthy were the marked edema of the small and middle-sized pyramidal cells in Lamina III of the agranular cortex, and the reduction in number of small cells in the red nuclei.

**Case II.**—The fourteen-year-old brother (P.P.) of the first patient was admitted on January 6, 1934, to Dr. T. McCrae's service, complaining of inability to swallow, double vision, slurring of speech, dizziness, and inability to walk.

*Family History.*—As noted in Case I.

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*Past Illnesses.*—Mumps, measles and "discharging ear" in early childhood, tonsillectomy at ten.

*Present Illness.*—The patient had been well, and attended

school on January 4th, but upon awakening at 6:30 A. M. next morning he experienced marked vertigo on standing. He returned to bed after eating breakfast. At 10 A. M., with no improvement, he visited the hospital, reporting also that his eyes were "hurting." The only positive finding on a careful physical examination was a mild conjunctivitis, but because of the vertigo he was kept at rest under observation until 5 P. M., when he was sent home with no new developments. That evening he vomited—an ill omen. He slept well but when awakened at 8 A. M. (January 6th) was unable to rise because of extreme vertigo. His eyes "hurt" slightly, there was lacrimation, and he could not swallow. He was returned to the hospital by ambulance. Nothing unusual about his diet could be determined, except for the mushrooms (*vide supra*) eaten January 1st.

*Physical Examination* (January 6th).—The patient was conscious and mentally alert; rectal temperature 99° F., pulse rate 115, blood pressure 126/104. There were present bilateral blepharoptosis (more marked on the left), mydriasis, diminished pupillary response to light, complete ophthalmoplegia and active corneal reflexes. The right corner of the mouth drooped slightly, but he was able to wrinkle the forehead and close the eyes firmly. The soft palate was completely immobile, and the tongue could be weakly protruded in the midline. Cutaneous perception of pain was normal. The hand clasps were weakened, but the power in the arms and legs was good; there was no incoordination, no muscular twitchings, and no convulsive movements. The biceps, triceps and patellar reflexes were active and equal; the heel-to-heel test was accurately performed. There was no characteristic Babinski sign on plantar stimulation, though all toes and the ankle were extended. The sensations of position, vibration and pain were intact. There was no stiffness of the neck, and no Kernig's sign. The abdominal and cremasteric reflexes were active but easily fatigued.

At this time the neurological signs were largely confined to the cranial nerves, especially the third, fourth, sixth, tenth,

and twelfth, with partial involvement of the seventh. There were no signs of meningeal irritation. The process indicated involvement of the base of the brain, especially the nuclei of the cranial nerves mentioned. Encephalitis, an abortive type of anterior poliomyelitis, or some intoxication were considered as possible causes.

January 7th.—Ptosis of the eyelids was almost complete; there was definite palsy of the muscles supplied by the seventh nerves, coupled with inability to wrinkle the forehead; he could open his mouth slightly, but could not retract the corners; the masseter muscles were active. The tongue was weaker—he could protrude only the tip and it deviated slightly to the right. Thoracic excursion was diminished, and respiration was abdominal in character. There was no weakness of the leg muscles. The abdominal and biceps reflexes were absent. The patellar reflexes responded only to repeated stimulation. There were no sensory changes. These signs suggested a progressive involvement of the spinal cord as well as the bulbar region.

On the morning of January 7th, the patient became cyanosed and the respiration more feeble. He was placed in the respirator, but the improvement was temporary. Death followed shortly, eighty hours after onset of symptoms. The pulse rate had increased to 132 before death, and the highest rectal temperature was 99.2° F. There was no bowel movement during his hospital stay. The patient's mental alertness was a striking contrast to his lethargic appearance, and persisted almost to the end. An autopsy was not permitted.

**Comments.**—Both patients had eaten mushrooms—as had the father who remained well—on January 1st. The onset of illness in Case I was about 10 A. M. January 2nd, and in Case II, 6.30 A. M. January 5th. The delayed onset of symptoms, the escape of the father, and the autopsy findings exclude mycetismus.

The first patient had eaten a "wiener" but her brother had not. The mother insisted that her own illness was an "ordi-

nary sore throat," and the infant brother, hospitalized elsewhere, had an acute upper respiratory infection.

That only two members of a large family should be poisoned, apparently on different days, suggests that probably the greater part of the noxious food was free of the toxin. This possibility has been stressed in another instance by McCaskey.<sup>17</sup> All members of the family had allegedly partaken of the same foods, except as noted above. Efforts to identify the source of the toxin were unsuccessful.

**Diagnosis.**—Encephalitis and mushroom poisoning were discarded in favor of anterior poliomyelitis of the bulbar type, despite the season of the year, and the simultaneous occurrence in siblings. Botulism was discussed, but the symptoms were considered in accord with acute bulbar poliomyelitis. This decision was finally reversed by exclusion of the latter at autopsy, and we are convinced that these were typical cases of botulism, though lacking bacteriological support of this diagnosis.

For completeness, it should be mentioned that cerebrospinal syphilis, toxic ophthalmoplegia, rabies, postdiphtheritic complications, poisoning with belladonna or methyl salicylate, and atypical Landry's paralysis may be confused with botulism.

The investigation and treatment, in retrospect, were incomplete; hence we present in more detail an outline of more adequate study of suspected cases of botulism.

**A. General.**—1. Obtain the assistance of municipal and state Boards of Health for an epidemiological survey, prophylactic immunization of other contacts, securing of antitoxin, etc.

2. By careful review of the diet, identify and, if possible, procure a sample of the responsible food for laboratory examination.

3. All other persons who ate the suspected food should be given immunizing doses of mixed antitoxin sera—2000 units of type A and 2000 units of type B—subcutaneously after testing for sensitivity.

4. If the responsible food has been commercially prepared, the manufacturer should be notified at once in order that other contaminated foods may be recalled. Suspected food may be rendered safe for further storage by adequate pressure cooking, or for ingestion by boiling immediately before consumption.

B. **Specific.**—1. The patient's stool and vomitus, as well as suspected foodstuffs, should be subjected to microscopic search for the organism in the stained smears, and to bacteriological cultures in anaerobic glucose media.

2. Inoculation of guinea-pigs, or preferably mice, with filtered aqueous solutions of food, vomitus, feces or intestinal washings containing the toxin will promptly reproduce the clinical manifestations as seen in man. Mice inoculated intraperitoneally will usually die within six hours. By giving one mouse the toxin alone, a second mouse toxin with type A antitoxin, and a third mouse toxin plus type B antitoxin, the specific serum may be quickly selected, and the strain of organism identified.

3. Chickens fed on the toxic material will develop "limber-neck" only if type A toxin be present, being refractory to type B toxin.<sup>15</sup>

4. Isolation of the toxin from the patient's blood is feasible. Citrated blood may be injected intraperitoneally into animals for this purpose.<sup>19</sup> Bergman *et al.*<sup>20</sup> identified the toxin in the blood of several patients by toxin-antitoxin experiments of this character.

5. At autopsy, the bacillus is most likely to be demonstrated in the brain,<sup>21</sup> spleen<sup>22</sup> and jejunal wall.<sup>14</sup>

C. **Treatment.**—1. Antitoxin. Before the strain is identified, 10,000 units of mixed (A and B) antitoxin sera should be given intramuscularly after preliminary testing for serum sensitivity; the same dosage of univalent serum is subsequently administered at twenty-four-hour intervals. If given before the toxin is fixed in the tissues, *i. e.*, before the onset of symptoms, the prognosis is good; otherwise it does not appear to alter the course of the disease, but even after symptoms appear,



it will neutralize the toxin present in the blood, or subsequently absorbed from the intestinal tract.

Botulinus antitoxin may be obtained from the Jensen & Salisbury Laboratory, Inc., Kansas City, Mo.; from the Hygienic Laboratory, Washington, D. C.; and from the Department of Health, New York City.

2. Absolute rest. The patient should be kept under the influence of morphine or sodium amytal after the diagnosis is made.

3. Diet. Liquids should be given freely with adequate calories (30 per kilogram of body weight) by nasal tube left *in situ*.

4. Gastric lavage. This is recommended if the patient is seen early. Oleum ricini, 1½ ounces, or magnesium sulphate, 1 ounce, may be left in the stomach.

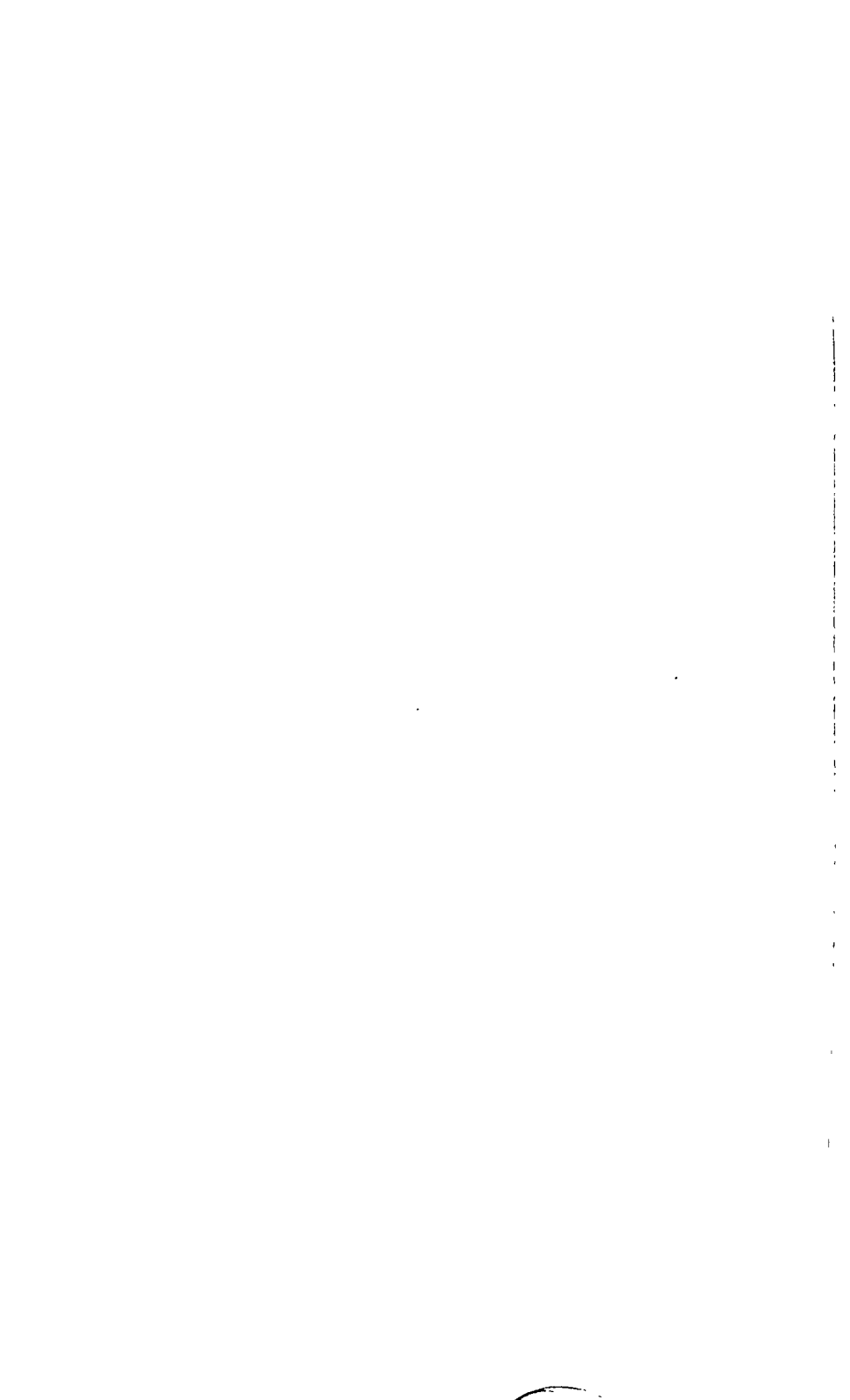
5. Enemata. Early evacuation of the intestinal tract is highly desirable.

6. Artificial respiration. Respirations may cease with little warning. The slightest signs of respiratory embarrassment indicate "respirator" treatment.

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## CLINIC OF DR. JOHN DURKIN

### METABOLIC CLINIC, PENNSYLVANIA HOSPITAL

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#### DIABETES MELLITUS AND HYPOTHYROIDISM WITH A REPORT OF A CASE

DIABETES mellitus complicated by hypothyroidism is rare and there is but a small literature on this subject. This is in contrast to 1.1 per cent of all patients with hyperthyroidism who have true diabetes (Wilder<sup>1</sup>).

Joslin<sup>3</sup> reported a case of myxedema with subsequent development of diabetes. The diabetes was readily controlled by dietetic treatment. Thyroid medication was continued by the patient according to her symptoms for eighteen months. During this time the diabetes seemed to become more severe. Hospitalization and insulin treatment were refused. Nevertheless a moderate diet prevented glycosuria. The basal metabolic rates varied from  $-32$  per cent before to  $+14$  and  $-9$  per cent after the onset of diabetes and during thyroid therapy. Another case<sup>3</sup> cited had diabetes for eleven years before the onset of myxedema. Basal metabolic determinations in this instance averaged  $-20$  per cent.

Holst<sup>2</sup> reported an improved tolerance for glucose in a diabetic who developed myxedema following thyroidectomy for exophthalmic goiter. Wilder<sup>1</sup> records improvement in tolerance in a diabetic child, aged three years, coincident with the development of myxedema. Growth was resumed but intense glycosuria and ketosis followed thyroid therapy. Growth ceased and the tolerance improved when thyroid treatment was stopped. This was so striking that the patient



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"could eat anything without excreting sugar." The child presented the appearance of juvenile myxedema, "the face dull and expressionless, the skin dry and thick, the hair coarse and scanty." The mentality and physical development were much retarded with a B. M. R. of  $-45$  per cent. There was no glycosuria and the blood sugar was 0.12 per cent. Thyroid extract was again administered in small doses and the metabolism raised gradually. The diet was rigidly restricted. When the B. M. R. reached  $-10$  per cent sugar appeared in the urine. Glycosuria continued—as much as 20 Gm. daily—and the fasting blood sugar reached 0.145 per cent, in spite of 10 units of insulin daily. This case, according to Wilder, lends support to the theory that with lower metabolic rates the tissue cells can utilize a given amount of glucose with less insulin than when the metabolism is at a higher rate.

Wright<sup>4</sup> presented 2 cases of myxedema and diabetes in which, contrary to the accepted theory, the administration of thyroid extract had no untoward effect on the action of insulin.

**Case Report.**—W. C., female, age thirty-eight, a servant, was admitted to the Pennsylvania Hospital October 14, 1935, complaining of: a craving for sweets, itching about the vulva, dizziness, flashes of light before her eyes, headache, constipation, loss of weight, frequent urination with nocturia and burning on urination, numbness, tingling in the legs and painful fingers.

The family history was irrelevant and her past illnesses consisted of scarlet fever, whooping cough and measles in childhood, pleurisy in 1917, influenza in 1918 and erysipelas in 1922. Her best weight was 82.7 Kg. (182 pounds) in 1925; she has had excessive thirst for many years and recently she has slept poorly.

**Present Illness.**—On August 27, 1935, rising to void at night, she became dizzy and fell, striking her head. Frontal headache and vertigo have been constant symptoms since. Increased appetite, frequency of urination, with large quantities of urine have been noted for many years but on September

23, 1935, she first noticed pruritus vulvae. This has persisted. Glycosuria was detected on October 10 and the blood sugar was 265 mg.

*Physical Examination.*—The points of note were: height, 62 inches; weight, 71.8 Kg. (158 pounds); blood pressure, 170/95; patient short and stout with some fulness of neck. Skin thickened. Left border of cardiac dullness 12 cm. from the midsternal line in the fifth costal interspace. Soft systolic murmur at the apex. Pulmonic second sound greater than the aortic second. Abdomen moderately obese.

*Laboratory Data:* see table, pages 282, 283.

*Discussion.*—This patient presented the appearance of having a moderately severe diabetes complicated by hypothyroidism. The diabetes, before standardization, was sufficiently severe to cause a loss of weight in spite of a low metabolism, the basal metabolic rate being  $-27$  per cent. Subsequently when the diabetes was controlled there was no loss of weight with a diet of 1100 calories. Following thyroid therapy, however, a decrease in weight ensued. During this treatment the diet and insulin were kept practically constant, the insulin averaging approximately 35 units daily. The blood sugar values varied from 0.265 to 0.08 per cent, and the weight steadily decreased from 155 pounds to  $137\frac{1}{2}$  pounds. The basal metabolic rate reached  $+31$  per cent. At this point it was decided to stop the thyroid medication and note the changes that ensued. In three months the weight increased to 150 pounds, higher than at the time of admission to the ward. The insulin was gradually decreased as the basal rate returned to the former level, the blood sugar dropped to normal, and the urine became practically sugar free. It would appear that on a continued restricted diet (1100 calories) this individual should be able to maintain her weight at about 150 pounds, and also remain fairly well standardized unless some factor such as an infection, thyroid therapy, pregnancy, fever or intoxication should complicate the picture. Any of these would elevate the metabolism and consequently larger amounts of insulin would be necessary.



Date, 1935.	Diet.				Blood sugar.	Glycosuria.				Insulin.			Weight	Thyroid	B. M. R.	Cholesterol	Remarks
	P.	F.	C.	Cal.		7	11	4	10	8	12	6					
10/14	65	47	130	1500	265	-	+4	+4	+4	0	0	0	148				B. S. on admission.
10/15					212	0	0	+4	+4	17	12	14					Fasting B. S.
10/17					207	+4	+4	+4	+2	23	12	17	150½				B. S. 1 hr after break- fast
10/19					180	+4	+2	+1	+1	27	17	23	153			253	
10/21	50	47	120	1100	161	+1	0	0	0	23	12	17					
10/23						+1	0	0	0	26	12	14	155				
10/28						0	0	0	0	23	7	16	153				
10/30					150	+1	0	0	0	23	7	13	151				
11/ 3					105	0	0	0	0	21	7	11	147				
11/ 5					101	+1	+2	0	0	21	7	11					
11/ 6					125	0	0	0	0	21	7	11					
11/11					119	0	0	0	0	21	7	13	146½				
11/12					138	0	0	0	0	21	7	13					
11/16					89	+1	0	+2	0	21	7	13	146				
11/19					100	0	0	+1	0	21	7	13	145				
11/20					100	0	0	0	0	21	7	13			-20%		
11/24					104	+2	+1	0	0	21	7	13	143½		RF. V -10%		
11/26						+2	+1	0	0	21	7	13	141		RF. V -25%	172	Discharged ward from

12/ 6	18	17	120	1100	156			0.5%		17	5	10	142	gr. viij			O. P. D.
12/13					169			0		14	7	12	138	gr. viij			B. S. 1½ hr. after breakfast.
12/20					131			0		14	7	12	138	gr. vi	-5%		
12/27					199			3.0%		16	9	14	138	gr. vi	+31%		
12/31																	
1936 1/ 3					197			0		16	9	14	137½	gr. iij			
1/10					121			0.7%		14	7	14	138	gr. iij	+6%		
1/20					146			0		12	5	12	138½	0			
2/ 3					169			0		12	5	12	142	0			
2/17					129			0		12	5	12	145½	0			
2/24					185			+		12	5	12	147½	0			
3/ 2					176			0		14	7	14	146	0	-5%		
3/16					80			0		14	7	14	150	0			
3/30					100			0		10	5	10	150½	0			

Date, 1935.	Diet.				Blood sugar.	Glycosurin.				Insulin.						Weight.	Thyroid	B. M. R.	Cholesterol	Remarks
	P.	F.	C.	Cal.		7	11	4	10	8	12	6								
10/14	65	47	130	1500	265	—	+4	+4	+4	0	0	0	0	148					B. S. 3.4 gm. per 100 cc.	
10/15					212	0	0	+4	+4	17	12	14							Fasting B. S.	
10/17					207	+4	+4	+4	+2	23	12	17		150½					B. S. 1 hr. after breakfast.	
10/19					180	+4	+2	+1	+1	27	17	23		153			253			
10/21	50	47	120	1100	161	+1	0	0	0	23	12	17								
10/23						+1	0	0	0	26	12	14		155						
10/28						0	0	0	0	23	7	16		153						
10/30					150	+1	0	0	0	23	7	13		151						
11/ 3					105	0	0	0	0	21	7	11		147						
11/ 5					101	+1	+2	0	0	21	7	11								
11/ 6					125	0	0	0	0	21	7	11		146½						
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11/12					138	0	0	0	0	21	7	13								
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11/20					100	0	0	0	0	21	7	13				—20%				
11/24					104	+2	+1	0	0	21	7	13		143½		—19%				
11/26						+2	+1	0	0	21	7	13		141		—25%	172		Discharged from ward.	

12/ 6	18	17	120	1100	156		0.5%	17	5	10	142	gr. viij		O. P. D.
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12/31														
1936 1/ 3					197		0	16	9	14	137½	gr. iij		
1/10					121		0.7%	14	7	14	138	gr. iiij	+6%	
1/20					146		0	12	5	12	138½	0		
2/ 3					169		0	12	5	12	142	0		
2/17					129		0	12	5	12	145½	0		
2/24					185		+	12	5	12	147½	0		
3/ 2					176		0	14	7	14	146	0	-5%	
3/16					80		0	14	7	14	150	0		
3/30					100		0	10	5	10	150½	0		

**Conclusion.**—This case serves to illustrate that by increasing the total metabolism with thyroid, the diabetes is made more severe. This has been noted by others.<sup>5, 6, 7</sup> When thyroid was stopped, the basal metabolism and in consequence the total metabolism was lowered and the diabetes appeared less severe and was more easily controlled.

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## CLINIC OF DR. MICHAEL G. WOHL

TEMPLE UNIVERSITY AND PHILADELPHIA GENERAL HOSPITALS

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### HYPERTHYROIDISM

#### AN EVALUATION OF BLOOD IODINE, IMPEDANCE ANGLE AND BASAL METABOLIC RATE IN BORDERLINE CASES

IN a survey of the hyperthyroid syndrome,\* certain basic facts should be borne in mind. First—while one is impressed at the bedside that many symptoms of Graves' disease may be attributed to other glands of internal secretion than the thyroid, such as the adrenal glands, the pituitary, etc., the fact remains that when the surgeon fails to remove sufficient thyroid tissue the patient will return after a certain interval of time with symptoms of hyperthyroidism, and when sufficient thyroid tissue is removed the second time, the symptoms will largely disappear. Therein lies a fact which is difficult to reconcile with Zondek's<sup>1</sup> so-called "peripheral theory" of the pathogenesis of Graves' disease. The recent follow-up study by Thomas and Rienhoff<sup>2</sup> of patients who were operated on for hyperthyroidism by removal of approximately nine tenths of the thyroid gland, shows that over 90 per cent of the cases were completely rid of their symptoms. The histological picture of the thyroid tissue was that of hyperplasia and hypertrophy. Then again patients dying of hyperthyroidism show, as the most outstanding anatomic finding, alterations in the thyroid gland almost to the exclusion of other organs. Even the enlargement of the thymus is not a constant finding, being pres-

\* For practical purposes the term "hyperthyroidism" includes Graves' disease or the toxic diffuse goiter as well as toxic adenoma or the toxic nodular goiter.

ent in only 15 per cent of the cases; and the structural changes in the liver in the form of well-marked hepatitis occurs only in about 54 per cent of cases.<sup>3</sup> Attempts to produce hyperthyroidism in man by injection of thyrotropic hormone of the anterior pituitary have been disappointing, although in animals this hormone is capable of producing hyperplasia of the thyroid, rise in metabolism and loss of weight.<sup>4</sup>

One therefore is forced to conclude that hyperthyroidism in man is associated with hyperplasia of the thyroid and that the removal of the greater part of the thyroid gland offers the best therapeutic approach today as it will result, in a great majority of patients, in a marked clinical improvement or cure.

The second fact to be considered is that the inherent capacity of tissues to respond to the thyroid stimulation varies in different individuals. This may explain why in some patients suffering from hyperthyroidism the outstanding symptoms will be referable to the cardiac and in others to the gastro-intestinal and in still another group of patients to the nervous system. This phase will be discussed in some detail later.

From a diagnostic point of view it is important to stress the fact that the outstanding physiological abnormality of hyperthyroidism is the derangement of the regulatory control of tissue oxidation. This is measured by the determination of the basal metabolic rate. Thyroid activity may be judged by another method. The thyroid gland functions as a regulator of iodine metabolism. The thyroid hormone, thyroxin, is high in its iodine content. It is apparent then that the level of blood iodine and the amount of iodine excreted in the urine may serve as a diagnostic aid in evaluating thyroid activity.<sup>5</sup> A similar analogy one finds in evaluating pancreatic function by the blood sugar level and the amount of sugar excreted in the urine. The average normal blood iodine content found by Mr. Charles Goss in my laboratory on a group of 15 patients without evidence of thyroid disease was 11 gamma per 100 cc. of blood (a gamma or microgram is 0.001 mg.). In 18 patients with toxic goiter, including both the diffuse and nodular

type, the blood iodine varied from 15 to 39 gamma; the basal metabolic rate ranged in these patients from plus 24 to plus 56 per cent. Similar observations have been made by other workers. It is interesting that no correlation between the clinical severity of the disease, the basal metabolic rate and the concentration of blood iodine was noted. One must also bear in mind the fact that in some patients there may be an abnormally high excretion of iodine and therefore the blood iodine level may remain normal (a negative iodine balance).

During the progress of these studies it was my impression that the method for blood iodine determination was too complicated and time consuming to prove of practical importance in the diagnosis of hyperthyroidism.\* Dr. D. Roy McCullagh<sup>6</sup> of Cleveland has described a method which appears to be relatively simple and accurate. I personally had no experience with it.

Recently a bioelectric method for diagnosis of hyperthyroidism has attracted attention. This procedure is designated by Brazier<sup>7</sup> as the determination of the impedance angle, and by Lueg,<sup>8</sup> Wohl<sup>9</sup> and others, as the polarization capacity of the skin. While, for the impedance angle, high frequency alternating current (20,000 cycles) is used, it is important to point out that the quantities measured by the different workers are closely related to the impedance of the body to an alternating current passed through the body.<sup>10</sup> Brazier found that "in thyrotoxicosis there is a very marked deviation from the normal, these cases giving very high values for the impedance angle." She also found that the severer the disease the higher the impedance angle. On the other hand we found that the polarization capacity of the skin was not correlated with the basal metabolic rate in every instance. After working on this problem for two years I feel that the method is pregnant with too many technical difficulties to prove of clinical value, especially in the borderline cases. Dr. Lahey in a personal communication to the author writes: "we have had as high

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as 29 per cent error in the cases of hyperthyroidism" (using the impedance angle).

For practical purposes the diagnosis of hyperthyroidism is to be made from the clinical manifestations of the patient and a marked rise in the basal metabolic rate. The classical symptoms of hyperthyroidism are appreciated by all of us. They are: loss of weight in spite of increased energy intake, loss of strength, hypersensitiveness to heat, the persistent tachycardia and the characteristic emotionalism; irritability and restlessness. The atypical case of hyperthyroidism presents difficulties in diagnosis because of its protean symptomatology which may mimic organic disease of the heart, gastro-intestinal disturbance and because the basal metabolic rate may not be within the expected range. An increase in the basal rate is generally accepted as an indication of a thyrotoxic state. It should be borne in mind, however, that there is a small group of patients with hyperthyroidism, whose basal rate remains normal. This might be explained as due to the fact that the test is taken during the quiescent period, either as the result of a spontaneous or an iodine remission. Again, there are persons who have normally a lower basal rate, and therefore a rate that would be considered normal in another individual, might indicate thyrotoxicosis in such a person. In one of our cases of hyperthyroidism, masked as paroxysmal tachycardia, the basal rates were plus 7, plus 9, plus 3 and minus 12. A thyroidectomy brought about an amelioration of the symptoms that differed in no way from that in thyroidectomized patients with similar symptoms and a high basal rate. This patient belonged to a group to whom operation has been denied, due to overestimation of the importance of the metabolic rate.<sup>11</sup> A similar experience was described by Morris.<sup>12</sup> One should, however, be cautious in diagnosing hyperthyroidism in a patient who has a normal rate; other signs of hyperthyroidism are to be carefully looked for in the confirmation of the diagnosis.

Some patients with tuberculosis, essential hypertension and cardiac decompensation may present confusing points of

similarity with hyperthyroidism. It is to be borne in mind that the basal rate determination may not prove of great help in these conditions, since it is frequently elevated. Thus in pulmonary tuberculosis (advanced) the basal rate may be as high as plus 30 per cent. In early tuberculosis, however, the basal rate is normal.<sup>13</sup>

It may be impossible at times to decide whether one deals with early hyperthyroidism or malignant hypertension. The tachycardia, loss of weight, and muscle weakness are not uncommon in hypertension. Still greater confusion may arise when there is a fulness of the eyeballs which may simulate exophthalmos. One patient in our series presented such a picture; and even after six weeks of close observation, it was extremely difficult to make a differential diagnosis.<sup>14</sup> The basal metabolic rate may not be of much help in such a case since in hypertension the basal metabolic rate may be elevated.<sup>15</sup> A high diastolic blood pressure is usually found in hypertension and not in hyperthyroidism. This point might prove of value in the differential diagnosis.

A useful procedure in establishing the diagnosis in cases with an elevated basal rate is to observe the specific effect of Lugol's solution.<sup>16</sup> A series of metabolic tests is made before iodine is administered. This is done in order to detect a possible drop as the result of the patient's training in taking the tests. On about the eighth day of treatment, a most characteristic drop in the basal rate occurs if the patient suffers from hyperthyroidism; the clinical status may not be noticeably improved. After iodine is discontinued there is a rise in the rate after some interval. This is almost conclusive evidence of hyperthyroidism.

Another group of patients in whom the basal metabolic rate is often elevated are persons suffering with cardiac decompensation. It may become necessary to decide whether the high basal rate may be due to a possible hyperthyroidism being the cause of the cardiac disturbance. The average increase in the basal rate in cardiac decompensation without hyperthyroidism, is said to be 39 per cent above normal.

In a group of 38 cases studied at the Philadelphia General Hospital, Dr. Harold Robertson and I found the average basal rate to be plus 30. In one of our patients with cardiac decompensation due to mitral stenosis and insufficiency, the basal rate during the period of decompensation averaged plus 26 per cent. After nine days of restoration of compensation, it came down to plus 5 per cent. An increase of the basal rate above 30 per cent should be considered as due to hyperthyroidism, rather than to cardiac decompensation unless dyspnea is very marked.

The most bothersome condition to be distinguished from hyperthyroidism is that of autonomic imbalance, especially when there is present a goiter, tremor, and loss of weight. Such conditions have often been erroneously classified as *formes frustes*. "Such patients," as McGregor puts it, "are so often the victims of overenthusiastic specialism, that they present the greatest goiter problem of today." I have been able to follow a number of such patients who have been operated upon, and in whom the results were disappointing.

It is apparent that treatment for "toxic goiter" in such patients does not lead to symptomatic cure. There is no patient for whom a thyroidectomy will do more harm than cases of this type; an unnecessary operation will often overthrow an already poorly balanced nervous system. The autonomic imbalance cases are closely associated with the asthenic constitution of Stiller, orthostatic albuminuria or *cor juvenum* (Chvostek). They frequently present cardiovascular complaints without any demonstrable cardiovascular pathology and symptoms of functional neurosis are constantly present. Thus palpitation, dyspnea, precordial discomfort, ready fatigability, faintness, vertigo, insomnia, increased perspiration, difficulty in swallowing, tremor, pallor and flushing are all too familiar symptoms that patients with autonomic imbalance present for a long time. They differ from cases of *formes frustes*, and the monosymptomatic hyperthyroidism in that there is no elevation of the basal metabolic rate and persistent tachycardia does not occur. The tachycardia is an out-

standing and constant feature of hyperthyroidism, and is present even during sleep. Boas<sup>17</sup> has recorded, with cardiometer, waking and sleeping heart rates in patients with hyperthyroidism, and in persons with neurogenic sinus tachycardia. He found that although during waking hours the heart rate of persons with neurogenic tachycardia approximates that of patients with Graves' disease, during sleep there is a distinct reduction of the heart rate, reaching minimum levels that approach those of normal (the minimum heart rate for males being 53 and that of females 58 per minute), while in hyperthyroidism there is little reduction of the heart rate during sleep.

A point of some importance is that the patient with neurocirculatory asthenia is apt to complain of symptoms regarding his neck, which symptoms may have been suggested to him. Thus, three such patients were referred to us from the Jackson clinic because of the feeling of constriction and difficulty in swallowing. Fluoroscopic and esophagosopic examinations showed no abnormal findings in the pharynx and esophagus. The hyperthyroid patient on the other hand rarely complains of a choking sensation. He usually gives a history of having been in good health until his present illness for which he seeks medical advice. He is hyperactive, optimistic as to his ability to do things, although he is soon forced to stop his work because of fatigue.

There are a number of patients suffering from hyperthyroidism many of whom are treated for something else with disastrous results. The reason for the erroneous diagnosis is that such patients have a paucity of pathognomonic signs of hyperthyroidism. Their symptoms are referable to gastrointestinal or cardiac system and unless one is goiter minded the diagnosis of hyperthyroidism is often overlooked.

I have reported a group of patients in whom the common denominator was heart disease and who were treated for auricular fibrillation, paroxysmal tachycardia, congestive heart failure, transient auricular flutter, angina pectoris respectively; the hyperthyroid syndrome was never predominant; indeed



they mimicked organic heart disease to such an extent that they were treated for months by the usual cardiac therapy of rest, sedatives and digitalis without improvement. Not until the real trouble was suspected to lie in the thyroid gland and compound solution of iodine, x-ray or thyroidectomy was instituted were they relieved of their symptoms.<sup>11, 14, 18</sup>

In one patient the symptoms of hyperthyroidism were masked as a spastic colitis. This latter case is of special interest to us since Drs. Wm. Egbert and Harold F. Robertson and I have observed three other patients with hyperthyroidism in whom abdominal symptoms simulating acute surgical catastrophe were noted. This latter observation will be the subject of a future presentation.

Another one of our patients was treated for angioneurotic edema of the eyelids and one patient was attending a diabetic clinic for two years and failed to respond to insulin therapy as anticipated. One patient developed an amenorrhea and vague nervous disturbances and was treated for essential hypertension. In one male patient impotence was the most outstanding initial symptom. The patient was treated for three months before the true nature of the condition was recognized. The cardinal signs of exophthalmic goiter in all of them were few or absent.

In the final analysis the diagnosis of hyperthyroidism will largely rest on the observer's judgment as to all the signs and symptoms and his experience with similar patients.

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## CLINIC OF DR. BERNARD I. COMROE

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### DIAGNOSIS OF DISEASES ASSOCIATED WITH EN- LARGEMENT OF THE LIVER OR SPLEEN

IN this discussion an attempt is made to point out the most probable causes of enlargements of the liver and spleen and to present the diagnostic procedures which have proved of most value.

An enlarged liver is usually easily palpated with the patient lying flat on his back, and the abdominal wall further relaxed by flexion of the knees. Muscular relaxation is sometimes obtained only after immersing the patient in a tub of warm water. The liver is generally felt most readily just outside the edge of the right rectus muscle. When the lower margin is palpated, one must not conclude that this organ is enlarged until he has determined by percussion that the upper border is in its usual position. In thin, ptotic individuals it is not unusual to find that the upper border of a liver coincides with the costal margin. Again, in patients with liver abscess, the enlargement of the liver may be chiefly upward. A normal sized liver may be displaced downward by pulmonary emphysema, pleural effusion, or subdiaphragmatic abscess; on the other hand, pathological lesions which may be confused with an enlarged liver include carcinoma of the stomach, especially with infiltration along the greater curvature, impacted feces or malignancy of the transverse colon, or a greatly

thickened omentum secondary to chronic inflammatory or neoplastic peritonitis; as all of these are directly or indirectly attached to the liver, they may also move with respiration.

The overlooking of a splenic enlargement is most often due to hasty and improper examination for this organ. Most individuals agree that the patient should be examined first while lying flat on his back, with the knees well drawn up, the abdomen exposed, the palpating hands warm, and one hand used posteriorly to exert upward pressure while the other hand attempts to feel the splenic edge slip from under the left costal margin during a deep inspiration. Several additional points may prove useful. The lower pole of a greatly enlarged spleen may be felt low in the abdomen, and not under the costal margin; a spleen not formerly felt may become palpable when the patient assumes the right lateral decubitus with the knees well drawn up. Some of the characteristics of an enlarged spleen are as follows: the examining fingers can not be passed between the enlarged mass and the left costal margin; one or more well-defined notches may often be felt on its lower mesial border; percussion will reveal that the dulness over the enlarged mass is continuous with the dulness over the splenic area in the ninth to the eleventh interspaces in the left mid-axillary line; with a certain amount of practice, the dulness over the normal spleen can often be percussed so that slight enlargements of this organ may be detected before the mass becomes large enough to be palpated. The descending colon does not lie in front of an enlarged spleen. This latter can be determined by percussion alone, or by percussion after insufflation of the colon with a small amount of air. A markedly enlarged spleen will usually cross the midline below the umbilicus.

Of the many tests of liver function, very few are of real value in differential diagnosis. With the exception of the van den Bergh reaction, little diagnostic aid is obtained from these; on occasions, the bromsulphalein dye test and the galactose tolerance test have been of slight assistance. The Takata-Ara reaction for the diagnosis of portal cirrhosis is not positive

until a late stage of the disease so that its use is quite limited. The multiple functions performed by the liver render it practically impossible for any one test to properly evaluate the amount or type of damage to that organ. In regard to splenic function, no test is yet available; possibly further work along the line of radiopaque media such as thorotrast may offer some lead in this direction.

Bleyer<sup>1</sup> has shown that slight enlargement of the spleen is common in apparently healthy infants and is thus of little or no diagnostic help at this time. He found the spleen to be enlarged in 8 per cent of infants up to the third month, in 25 per cent from the third to the ninth month, in almost 20 per cent during the remainder of the first year, and in 9 per cent during the second year. He also pointed out the frequency of an enlarged spleen in childhood infections (measles, pneumonia, pertussis, syphilis, otitis media, tonsillitis, rickets, impetigo, rubella, eczema) and emphasized the infrequency of such an enlargement in so-called "simple" malnutrition. In an examination of the autopsy records of 14,000 patients, Barron and Litman<sup>2</sup> found that the diseases most frequently accompanied by marked splenic enlargement (of 600 Gm. or over) in adults were: leukemia, subacute bacterial endocarditis, portal cirrhosis, and Hodgkin's disease. Of spleens weighing 1400 Gm. or over, practically 80 per cent were found in patients diagnosed leukemia. They also found that the commonest causes of definite palpable enlargement of both liver and spleen in adults were: leukemia, gumma, subacute bacterial endocarditis, puerperal sepsis, typhoid fever, Hodgkin's disease, and portal cirrhosis. Concerning the frequency with which these diseases are encountered in the hospital wards, during the past two years there have been admitted to the medical clinic 23 patients with Hodgkin's disease, 21 with leukemia, 21 with portal cirrhosis, 18 with pernicious anemia, and 14 with subacute bacterial endocarditis.

A table attempting to classify the causes of hepatic enlargements is as follows:

## HEPATIC ENLARGEMENTS

I. *Cardiac Decomensation.*II. *Cirrhoses* (portal, toxic, obstructive biliary, luetic, carcinomatous, hypertrophic biliary—Hanot's, polyorrhomenitis multiple serositis, Banti's syndrome, hemochromatosis, eclamptic, carbon).III. *Tumors*A. *Benign* (adenoma, angioma, cavernoma, lymphangioma, myxoma, fibroma, lipoma).B. *Malignant* (carcinoma, melanosarcoma, chorionepithelioma, sympathetic neuroblastoma, teratoma, embryoma).C. *Cysts* (blood and degenerative, dermoid, endothelial, hydatid, lymphatic, etc.).IV. *Inflammations*

A. Acute pylephlebitis.

B. Hepatitis (septicemia, Weil's disease, relapsing fever, yellow fever, secondary syphilis, arsenicals, chloroform, phosphorus, pennyroyal, extract of male fern, naphthol, potassium chlorate, arseniureted hydrogen, atophan (cinchophen), mushroom poisoning, tuberculous, schistosomiasis, streptococcic, etc.).

C. Abscess (single, multiple, amebic).

D. Syphilis, malaria, typhoid fever, actinomycosis, kala-azar.

E. Slight enlargement, cloudy swelling, may occur in any septic disease.

V. *Blood Dyscrasias*

A. Leukemia.

D. Pernicious anemia.

B. Hodgkin's disease.

E. Sick cell anemia.

C. Hemolytic icterus.

F. Polycythemia.

VI. *Metabolic*

A. Gaucher's disease.

B. Niemann-Pick's disease.

C. Amyloidosis.

D. Von Gierke's disease.

E. Fatty liver.

F. Diabetes mellitus.

It is not possible in this article to describe the clinical pictures presented by these diseases; however, several facts may be of assistance. The hardest livers to palpation are generally produced by carcinoma. It is not well known that a primary or secondary carcinoma of the liver is sometimes accompanied by a quite high fever, may run its entire course without pain, not uncommonly is accompanied by a leukocytosis up to 15,000, and frequently produces no jaundice; however, malignancy is one of the most frequent causes of a long-standing jaundice. An enlarged tongue of liver known as Riedel's lobe may occasionally be found protruding from under the right half of the liver. This may be confused with almost any abdominal tumor on the right side of the abdomen; an alleged Riedel's lobe usually turns out to be nonexistent, most often proving to be a gallbladder mass.

Several factors may prove useful in determining the etiology of a hepatic enlargement. These are:

1. The presence or absence of jaundice.
2. Ascites.
3. The size and shape of the liver.
4. The association with splenic enlargement.

Those diseases with hepatic enlargement which are usually accompanied by little or no obvious jaundice are: cardiac decompensation, liver abscess, leukemia, polyserositis, Banti's syndrome, amyloid disease, and fatty liver. Hepatic enlargement with ascites is most frequently encountered in: malignancy, portal cirrhosis, cardiac decompensation, polyserositis (Pick-Concato's disease), Banti's syndrome, syphilis of the liver, and amyloid disease; it is uncommon in leukemia, Hodgkin's disease, pernicious anemia, and polycythemia. A very large liver is produced usually by primary or secondary tumor (carcinoma, melanoma, angioma), Hodgkin's disease, amyloidosis, and leukemia. The finding of a fair degree of enlargement of both spleen and liver should suggest: leukemia,



subacute bacterial endocarditis, Hodgkin's disease, puerperal sepsis, typhoid fever, portal cirrhosis, septicemia, amyloidosis, melanosarcoma, and possibly pernicious anemia.

The following table is an attempt to enumerate in so far as possible the causes of splenic enlargement.

## SPLENIC ENLARGEMENT

### I. *Circulatory*

- A. Thrombosis of the portal vein or its branches.
- B. Pericarditic pseudocirrhosis of the liver.
- C. Chronic cardiac decompensation in infants.
- D. Cirrhosis of the liver.

### II. *Infections*

- A. Typhoid and paratyphoid fever.
- B. Malaria.
- C. Subacute bacterial endocarditis; malignant endocarditis.
- D. Septicemia.
- E. Undulant fever.
- F. Other acute infections (rheumatic fever, poliomyelitis, influenza, erysipelas, tularemia, relapsing fever, typhus fever, Rocky Mountain spotted fever, pneumonia, Weil's disease).
- G. In children: measles, pneumonia, active rickets, active syphilis, pertussis, otitis media, impetigo, diphtheria, rubella, Still's disease.
- H. Chronic ulcerative colitis.
- I. Tuberculosis and syphilis.
- J. Felty's syndrome.
- K. Abscess of the spleen.
- L. Tropical diseases (kala-azar, Chaga's disease, sleeping sickness, bilharziasis).
- M. Lupus erythematosus (acute or generalized).
- N. Pylephlebitis.
- O. Hepatitis.

III. *Blood Dyscrasias*

- |                              |   |
|------------------------------|---|
| A. Leukemia.                 | H. Cooley's erythroblastic anemia.      |
| B. Hemolytic icterus.        |   |
| C. Purpura hemorrhagica.     | I. von Jaksch's anemia.                 |
| D. Infectious mononucleosis. | J. Pernicious anemia.                   |
| E. Hodgkin's disease.        | K. Banti's syndrome and splenic anemia. |
| F. Sickle cell anemia.       |   |
| G. Polycythemia vera.        | L. Agranulocytic angina.                |

IV. *Metabolic Disturbances*

- |                            |                     |
|----------------------------|---------------------|
| A. Gaucher's disease.      | E. Amyloidosis.     |
| B. Niemann-Pick's disease. | F. Hemochromatosis. |
| C. Xanthomatosis.          | G. Lipoidemia.      |
| D. Hypercholesterolemia.   | H. Toxic goiter.    |

V. *Primary Tumors*

- A. Benign (hemangioma, fibroma).
- B. Malignant (sarcoma, lymphosarcoma, reticulum cell sarcoma).
- C. Cysts (hydatid, dermoid, simple, lymphangioma, hemangioma, posttraumatic, hemorrhagic, multiple congenital).

VI. *Unclassified*

- A. Status lymphaticus.
- B. Congenital hydrops (infants).
- C. Giant lymph follicle hyperplasia.
- D. Congenital hematorporphyria.
- E. Albers-Schönberg disease (marble bones).
- F. Movable spleen.
- G. Normal splenic enlargement in infancy.

Splenomegaly should arouse one's curiosity concerning the following points:

- |                     |                         |
|---------------------|-------------------------|
| 1. Lymphadenopathy. | 4. Blood picture.       |
| 2. Jaundice.        | 5. Fever.               |
| 3. Ascites.         | 6. Hepatic enlargement. |

Diseases associated with splenomegaly which usually present lymph node enlargements are: lymphatic leukemia, Hodgkin's disease, infectious mononucleosis, status lymphat-

icus, lymphosarcoma, Still's disease, some of the acute exanthemata, tuberculosis, septicemia, leukosarcoma, tularemia, syphilis, giant lymph follicle hyperplasia and, very rarely, myelogenous leukemia. Splenic enlargement and ascites should suggest portal cirrhosis, Banti's syndrome, portal thrombosis, amyloid disease, syphilis of the liver, perihepatitis, cardiac decompensation in children, and, occasionally, leukemia, Hodgkin's disease, von Jaksch's anemia and polycythemia. Splenomegaly together with jaundice is seen in hemolytic icterus, Hanot's cirrhosis (and occasionally, 25 per cent of cases, in portal cirrhosis), septicemia, syphilis of the liver, pernicious anemia, yellow fever, malaria, and Weil's disease; jaundice is somewhat uncommon in leukemia, Hodgkin's disease, Banti's syndrome, typhoid fever, and pneumonia. If leukopenia is found, the diseases to be considered will include: pernicious anemia, Banti's syndrome, Gaucher's disease, aleukemic leukemia, agranulocytic angina, typhoid and paratyphoid fevers, malaria, undulant fever, overwhelming infections, measles, kala-azar, and occasionally Hodgkin's disease. If fever accompanies the splenomegaly, one must think of malaria, typhoid and paratyphoid fevers, leukemia (especially the acute form), undulant fever, subacute bacterial endocarditis, Hodgkin's disease, infectious mononucleosis, acute exanthemata, tularemia, typhus fever, Rocky Mountain spotted fever, kala-azar, acute pyelophlebitis, some cases of hepatitis, and occasionally of pernicious and other severe anemias.

Laboratory tests which might be of aid in the differential diagnosis of conditions producing hepatic or splenic enlargement include:

1. Complete blood count: red blood cells, white blood cells, differential, platelets, reticulocytes, search for parasites (malaria, etc.).
2. Examination for macrophages in blood from lobe of ear.
3. Examination for sickling phenomenon.
4. Urinalysis: routine, bilirubin, urobilin, and bile salts.
5. Blood Wassermann reaction.

6. Bleeding time, coagulation time, clot retraction, tourniquet test, volume index.
7. Fragility of the red blood cells.
8. Paul's heterophile antibody test (in diagnosis of infectious mononucleosis, aleukemic leukemia, etc.).
9. Blood agglutination tests: typhoid fever, paratyphoid fever, undulant fever, typhus fever, tularemia.
10. Blood culture.
11. Blood cholesterol, sugar, van den Bergh.
12. Congo red test (possible aid in diagnosis of amyloidosis).
13. Echinococcus complement fixation test.
14. Lymph node or sternal bone marrow biopsy.
15. Gordon test for Hodgkin's disease.
16. Blood viscosity test (in polycythemia).
17. Splenic puncture (of doubtful value).
18. Roentgen examination of the skull and long bones (may be useful in diagnosis of Gaucher's disease, Hodgkin's disease, Cooley's anemia, syphilis, rickets, leukemia, metastatic malignancy, Albers-Schönberg disease, etc.).

A few additional remarks concerning the above tests might prove of value. As regards the differential blood count, the presence of splenic enlargement together with an eosinophilia would suggest echinococcus disease, myelogenous or eosinophilic leukemia, Hodgkin's disease, bilharziasis, scarlet fever, or a postfebrile state. Pepper and Farley<sup>3</sup> consider basophilia to be of little diagnostic importance. A lymphocytosis with splenomegaly would call to mind the possibility of infectious mononucleosis, whooping cough, Malta fever, chronic lymphatic leukemia, or possibly toxic goiter or typhoid fever, while an increase in monocytes may be found in subacute bacterial endocarditis, various septicemias, Hodgkin's disease, malaria, monocytic leukemia, etc. A thrombocytopenia may occur in purpura hemorrhagica, acute lymphatic leukemia, kala-azar, pernicious anemia and possibly in some hepatic diseases; thrombocytosis with splenic enlargement has been found in polycythemia, chronic myelogenous leukemia, and Hodgkin's disease. A persisting elevation of reticulocytes should sug-

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gest hemolytic ictero-anemia; it is also of diagnostic importance in the remission of primary pernicious anemia. Another diagnostic aid is the search for macrophages in a drop of blood obtained from the lobe of the ear after massage of that part; macrophages may be found under such conditions in typhoid fever, subacute bacterial endocarditis, and possibly in leukemia and malaria. The presence of sickle cells is of course the important hematologic feature of drepanocytosis; these must be searched for in the usual manner by excluding the blood from oxygen for several hours.

The occurrence of urobilin in the urine in the absence of bile pigments and bile salts is a feature of hemolytic icterus. The prolongation of the bleeding time, normal clotting time, poor or absent clot retraction, and positive tourniquet test are well-known points in differentiating purpura hemorrhagica from hemophilia; in the latter, the clotting time is quite prolonged. Demonstration of increased fragility of the red blood cells is essential to the diagnosis of hemolytic icterus.

During the past several years, the introduction of the heterophile antibody test has been of great aid in clinching the diagnosis of infectious mononucleosis. The test is easily performed in any clinical laboratory; agglutination of sheep cells in a dilution of more than 1:16 is pathognomonic of infectious mononucleosis. The only other condition giving a positive test is serum sickness. It has recently been shown that agglutination in only a very low titer is a common occurrence in leukemia.

The value of the Congo red test in the diagnosis of amyloid disease is still open to question; however, a positive reaction is usually indicative of amyloidosis. The Gordon test for Hodgkin's disease (with introduction of macerated lymph node into the brain of a rabbit) is also not fool-proof; recently, positive reactions have been reported in various other diseases.

By careful selection of the appropriate tests in any given case together with a painstaking history and complete physical examination, one should readily be able to arrive at a correct diagnosis.

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## CLINIC OF DR. EDWARD L. BAUER

### JEFFERSON MEDICAL COLLEGE

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#### SCARLET FEVER TODAY

THE laboratory and clinical attack upon scarlet fever that has been so intense since 1925 was stimulated by the claims of the Dicks in 1924 of an etiological factor, the *Streptococcus hemolyticus scarlatinae*, with its toxin and an antitoxin. So much of the laboratory work done on this disease has been presented to the clinician that the clinical aspects have become secondary in his mind. Again he has been confused by the positiveness of diametrically opposite conclusions presented by numerous research workers.

The clinical aspects of the disease can be profitably enumerated since there is no real pathognomonic sign to identify scarlet fever save the possibility of the Schultz-Charlton reaction. This reaction is of value only in the early stage of the rash and only if convalescent serum is used to make the test.

The disease is ushered in after a three- to eight-day incubation period by fever from 101° to 104° F., sore throat about which many children will never complain, and nausea or vomiting which may not occur. Headache, malaise, and chills, or even convulsions in spasmophilic youngsters may or may not occur. Certainly this is not a specific picture of anything. The radial pulse is disproportionately rapid as compared to any degree of temperature that might be present.

Upon examination the tonsils, the pillars, and the soft palate including the uvula will show some degree of injection or erythema. More marked cases will show an intensely reddened throat with punctate red spots over the soft palate.



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An interesting phenomenon concerning the rash is its characteristic but not pathognomonic response to stroking. A white line will appear when the skin is stroked which disappears then reappears and persists for some time. This is called secondary pallor. In fact, constrictions in clothing, such as circular garters, will leave a persistently blanched area. Rumpel-Leede's sign, while not pathognomonic, can be elicited. This is done by applying a fairly tight tourniquet above the elbow causing petechial hemorrhages below. Any degree of itching may occur and an urticaria may accompany the rash.

Leukocytosis occurs in scarlet fever with an eosinophilia. The hemolytic streptococcus can be recovered from the throat and sometimes from the blood stream.

Desquamation may not follow a mild rash. Generally this phenomenon begins in the second or third week and starts on the dry skin in pin-point spots. The loosened serrated edges fusing with other similar areas make irregular patches or strips of peeling skin. Most characteristic is the loss of skin about the fingers and toes, the desquamation going out from the free ends of the nails causing casts of the ends of the fingers that may involve the whole hand, particularly if it is bandaged. The nails may become dry and wrinkled and as they grow out a definite line of demarcation will be seen separating the affected from the healthy nail. It must be remembered however that desquamation is not limited to scarlet fever since branny desquamation may follow measles and the scarlatinal type be reproduced in dermatitis exfoliativa and in other conditions where miliary vesiculation appears.

Scarlet fever may be very mild, so much so that the throat signs may be indifferent, the tongue signs absent, the rash fugacious and its characteristics elusive. The temperature may not go up to any appreciable degree even though the rash may be easily recognized. On the other hand cases of moderate severity will be easily identified by many if not all of the features portrayed. Severe and fulminating cases oc-

The tonsils may be covered with a gray or yellow exudate that when spotty suggests pus.

The tongue will generally be coated. In a few hours the papillae will become swollen and in the beginning particularly on the edge and on the tip they will peep through the coat. Later this occurs over the surface of the tongue giving the appearance of the surface of a raspberry but designated by most American writers as a "strawberry tongue." However in some mild cases of scarlet fever the tongue goes unscathed. As the coating comes off with desquamation the tongue is a deep red and the swollen papillae will stand out giving the appearance of a mulberry. Should this occur it is an aid to diagnosis after the rash has disappeared and before desquamation begins. In marked cases small white spots may be found on the gums that resemble phenol burns.

A general adenopathy occurs and persists, the inguinal glands being among the first that are palpable. In from twelve to seventy-two hours the rash appears although in many cases there is no rash. Only in the severest cases does a typical rash show itself on the face and then on the forehead and under the eyes. Ordinarily the cheeks are flushed with pallor around the alae of the nose and the upper and lower lips. This is the circumoral pallor not always seen in scarlet fever and sometimes seen in other conditions. The rash is first seen beneath the ear and chin lines and beneath the clavicle from which it distributes itself over the remainder of the body with fair rapidity. It may persist from three to seven days before fading out. The rash is essentially diffuse and punctate on an erythematous background. In blondes it is a vivid scarlet and in the more deeply pigmented it becomes duller. In the distinct brunette it has a coppery tinge. It is markedly coppery in the negro. The pores become swollen and stand out and miliaria appear. While the rash is generally evenly distributed in most severe cases, in the milder, tiny areas of healthy skin are scattered over the body. In fact in some few cases large patches of normal skin will be seen between scarlatinal areas. The rash will be found most intense in skin folds. In the an-

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casionally occur. In these cases the throat will be edematous and almost closed. The temperature will reach the higher ranges. The mucous membranes and skin may become hemorrhagic. Upon one occasion I saw five children in one family perish in twelve hours from the onset of their symptoms.

If the streptococcus and its toxin are to be accepted as the cause of scarlet fever then the general run of complications are not complications in the strict sense of the word but variants in the clinical manifestations of the disease. It is true that these manifestations are streptococcic in origin, whether a streptococcic toxin, some other organism with which the streptococcic organism works in symbiosis, or whether they follow in the wake of an allergic phenomenon. Only casual attention is paid to the adenopathy unless the cervical glands become perceptibly enlarged, cause distress, or suppurate as they sometimes do. Cervical adenitis may occur early or late. Suppurative middle ear disease frequently occurs and I have seen it cause much pain and distress even before the rash has put in an appearance. Mastoiditis may occur almost immediately following an otitic infection but generally takes about a week to develop.

While the nasopharynx was not mentioned when the characteristic picture of the throat was described evidence of infection is always present. Sinus involvement occurs which, should it persist, will in the third or fourth week or even earlier be accompanied by a nasal discharge or at least a moisture from which the hemolytic streptococcus can regularly be cultured.

Up to the third week endocarditis, pericarditis, pancarditis, pneumonia, pleurisy, empyema, multiple arthritis, multiple abscesses, appendicitis, peritonitis, osteomyelitis, and meningitis may occur, or any combination thereof. Nephritis occurs more frequently perhaps but occurs ordinarily late. The first evidence of nephritis may be found in the urine, albumin, blood, and casts appearing. Some apathy or irritability may be present. This may be followed rapidly by edema, in other cases by anuria with later edema and unconsciousness. Many

of the more toxic cases with high temperature may be delirious but the meningitis cases present the characteristic physical findings of this condition with a cloudy spinal fluid, increased cell count, and streptococci. The other aforementioned conditions present no picture that diverges from their occurrence without scarlet fever. It is evident that in scarlet fever we have a situation that is developed as a result of the combination of a bacterium and a toxin or allergic element or a toxo-allergen. Yielding to the toxin for a moment the rash, the picture of the tongue, the temperature, and perhaps the vomiting can be regarded as the work of the toxin. The temperature might also be caused by bacterial invasion. Certainly the pathology of the throat is a bacterial manifestation. The other phases commonly referred to as complications are undoubtedly bacterial. I personally do not believe that the nephritis should be excluded from this category in all instances. On the other hand there is much evidence to show that there are allergic characteristics present in the rash and obviously the toxo-allergen theory would have a strong leg to stand upon.

Occasionally there occurs an encephalitis beginning with headache, nausea, vomiting, then stupor, and even unconsciousness. Rigidity of the neck is always present but other signs of meningeal irritation change from hour to hour. Paralysis for some period of time is apt to occur in any extremity. The spinal fluid is clear under pressure with a moderate increase in cells, the polymorphonuclear variety predominating. No organisms are demonstrable. There is a high mortality to this encephalitis but if the patient recovers none of the post-encephalitic sequelae found after epidemic encephalitis occur. It is indeed a picture that parallels in its exactness the virus encephalitis which follows occasionally in the wake of small-pox vaccination, measles, and chicken pox. Here again is evidence for the adherents of the symbiotic group of etiologists.

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Before beginning a discussion of the treatment of scarlet fever an appraisal of the investigations into the cause and

serologic aspects should be noted. The controversies that have arisen over the *Streptococcus hemolyticus scarlatinae* which undoubtedly plays a big rôle in scarlet fever, the Dick toxin, and the antitoxins of Dick and Dochez demand scrutiny. The place of convalescent serum must also be established as far as possible.

Ever since the bacterial etiology of scarlet fever have been suspected the streptococcus has been accused. Schleissner, Gabritschewsky, Moser, Dochez, and then the Dicks have claimed a streptococcus and toxin as the cause of scarlet fever. The *Streptococcus hemolyticus scarlatinae* has several strains. The toxins produced by all the strains are not entirely related. Some of the commoner strains are most frequently associated with the mild scarlet fever prevalent in the United States in the last ten years. In the malignant scarlet fever occasionally seen other strains of streptococci are found and the toxins of the former strains do not seem to bear any relation to them.

The Dicks have devised an intracutaneous test for susceptibility to scarlet fever, using the toxin of their *Streptococcus hemolyticus scarlatinae*. Some of the more malignant cases of scarlet fever have occurred in individuals who were Dick test negative. Coste, Zoeller, and di Gröer have found that the test is variable in up to 40 per cent of individuals. It has been demonstrated that a negative test to one strain of toxin does not mean immunity to all strains. I have found positive reactors in 30 per cent of a group of children three years after bona fide attacks of scarlet fever. This is too high a percentage to be a true indication of susceptibility following scarlet fever in the light of clinical experience.

It has been clearly demonstrated that the Dick test does not measure blood antitoxin content. That it depends entirely upon local conditions is the claim of some and upon allergy of others. Ando first separated the toxin into a heat labile and a heat stable toxin. The former has toxic properties, the latter allergic properties.

Recently there has been an increasingly plaintive plea for more accurate standardization in the strength of toxin pro-

duction. The skin test dose of a given toxin seems to vary at present. This coupled with the aforementioned causes of error including the not unimportant variety of strains certainly nullifies the reliability of the test in given individuals.

The active immunization of individuals by the injection of multiple doses of toxin is also advocated by the Dicks. Negative Dick tests follow this effort at immunization. Some individuals have been known to remain negative two years or more. It appears however that this is a vaccinal immunity and if permanency is desired repeated series of injections must be given. Immunity to one strain of toxin does not necessarily confer immunity to all strains.

The reaction to these injections may entail more suffering particularly on the part of older people than scarlet fever itself. An attempt has been made to overcome this by giving smaller doses in greater number than the five prescribed by the Dicks. Since the skin test dose is not a reliable standard this may prove to be a snare or delusion.

The symptoms to be looked for are headache, nausea, vomiting, fever, a scarlatinal rash, sometimes edema and even anasarca, and pretty generally a painful cellulitis at the site of injection.

Evidence of more and more failures to prevent scarlet fever by the use of Dick toxin accumulate while others are positive in their statement that they have never had a failure. This latter is incredible because of the lack of standardization of material and the evident inability to immunize against all strains at one time. The answer seems to lie in the fact that success may attend where only one strain of streptococcus and toxin is present in a given community.

Since immunization with toxin deals exclusively with toxin in a disease in which the organism itself plays a more important part than the toxin the back door remains wide open while the front door is padlocked. This is demonstrated by the fact that cases of scarlet fever sine exanthemata can and do occur in the immunized. In these cases bacterial variants or complications have the same open sesame that they have



in those accompanied by toxemia and rash. With a population highly immunized to the toxin apparently more difficulty will be found in recognizing these cases and they will therefore become more numerous because of a lack of isolation precautions. It will necessitate the careful culturing of all sore throats and the definite identification of the almost omnipresent streptococcus as the Dick streptococcus or another streptococcus. This is by no means easy and certainly not the final word in the solution of this invited public health problem.

Efforts of this nature have already met with signal failure. For example, even with a diagnostic rash to help them O. Bauer and Minkerewitsch in an attempt to detain all scarlet fever carriers, that is, *Streptococcus hemolyticus scarlatinae*, so as to prevent return cases to a contagious disease hospital made no more impression on the number of such unfortunates despite more than 30,000 examinations.

By different technics Dochez and the Dicks both produced an antitoxin. The Dochez antitoxin also carries with it bacteriocidal properties. The Dick antitoxin does not. From the discussion of the clinical picture of scarlet fever a bacteriocidal agent is as important as an antitoxin.

The use of the Dick antitoxin in the treatment of scarlet fever has been followed by a rapid decline in the temperature and an almost sudden release from toxic manifestations. Authorities differ upon the reduction in the number of complications. That they continue to occur is certain and since there is controversy concerning this claim it must be understood that more than simple statistics are necessary before any conclusions can be drawn. To date it must be said that no publications claiming marked reductions in complications have had complete and iron-clad control studies. Otherwise there should be no difference in similarly controlled experiments such as now exist.

Because of the severe reactions to the antitoxin itself and the relatively high proportion of anaphylactic deaths following its use most workers now use the antitoxin simply for se-

vere cases. A more concentrated serum is now available which the producers claim cuts down the protein reactions and they urge its use in the mild as well as severe cases. Its value has yet to be clinically established for not enough work has been done with it to justify all the claims made for it. This fact must be borne in mind particularly in dealing with the milder cases, that if the disease is abruptly terminated there will be far less antibody response and consequently fewer individuals develop immunity to the disease by reason of their attack.

Another unfortunate fact about scarlet fever antitoxin is its lack of standardization. The substitution of antitoxin for convalescent serum in the Schultz-Charlton test led me to try the antitoxin of three commercial houses simultaneously in individual cases in a series of patients of unquestioned scarlet fever. By way of parenthesis, the Schultz-Charlton reaction is the blanching of a rash in a scarlet fever patient about the site of an intracutaneous injection of convalescent scarlet fever serum. In the test there has been substituted antitoxin for the convalescent serum.

I shall present five cases of my series upon whom three blanching tests were attempted simultaneously in each case and all five cases being tested on the same day with the same products. The result can be graphically expressed as follows:

Antitoxins Nos.	1	2	3	
1.	+	—	+	
2.	+	—	+	(+ = blanching)
Patients { 3.	—	—	+	(— = no blanching)
4.	+	—	—	
5.	+	—	—	

These antitoxins by their expiration date had been but recently issued. This series has been duplicated in its inconsistent results by comparison of other scarlet fever antitoxins in other groups of patients. Obviously the experiment relegates the Schultz-Charlton test to pooled convalescent sera if accuracy in diagnosis is sought. It also places the clinical results obtained in the use of some scarlet fever antitoxins in the category of nonspecific protein therapy or in the realm

of the weakness of clinical observations caused by that sometimes human frailty, unbridled enthusiasm. I believe that there is more than a mere leg to stand upon in support of the former premise.

The immunization of contacts with scarlet fever patients is worthy of some discussion. Since so many contacts presumably susceptible fail to contract the disease upon exposure it is not reasonable to presume that immunization either with antitoxin, toxin, or a combination of toxin and antitoxin has protected in isolated instances. In institutions or in hospital wards contact may not have actually occurred as in households for everyone has seen sporadic cases of scarlet fever even in these environs without secondary cases. On the other hand, if these secondary cases actually occur in those upon whom immunization has been attempted then some reason must be sought for the failure.

In 1925, 1926, and 1927 I had five such experiences in three hospitals, that is, secondary cases arising in children who had received prophylactic doses of Dick scarlet fever antitoxin. From then until 1931 I attempted to immunize by a combination of Dick toxin injections following a prophylactic dose of the antitoxin. This proved futile in three instances. Since then I have used neither. Curiously enough, perhaps to establish the vagaries of statistical conclusions, I have had seven sporadic cases in various wards with no secondary cases and no attempt was made at immunization.

In institutions I have attempted to segregate Dick positives and Dick negatives with no appreciable difference in the occurrence of secondary cases in either group. Not that I have not found groups of Dick negatives without secondary cases but there have also occurred Dick negative groups where cases did develop and Dick positive groups where they did not develop. By continuing this over a period of seven years I have come out even.

The immunization of institution children with the Dick toxin has led to an increase in the number of scarlet fever sine exanthemata cases and a number of cases of scarlet fever

with rash. I have experienced no benefit over a long period of time from any form of scarlet fever immunization and in from seven to ten years instead of wholehearted enthusiasm I am overwhelmed with morbid pessimism.

The customary answer is that the technic was faulty, the toxin rendered inert by faulty manipulation, or that it lacked proper standardization. On the first two counts I have adhered strictly to the Dick technic, and on the third I have used nothing but the materials covered by the Dick patents and standardized under their regulations.

To sum up the serologic aspect I confess that I am fascinated by something still elusive in this branch of scarlet fever study. To lay a new and good foundation the patents should be forever waived and the subject returned to the laboratories so that the bacteriologist and serologist will have complete freedom for all manner of study within their ken. With this fresh, unfettered effort will the key be found.

Enough has been said about serology in scarlet fever to justify our lack of faith in Dick antitoxin as a curative agent. True, I repeat, it shortens the acute stage. I have seen the same thing happen when other antitoxins or horse serum have been used. The use of pooled convalescent scarlet fever serum is effectual when given in large doses.

There is undoubtedly the additional element of bacteriocidal potency but this varies with different lots of serum. Should an attempt be made to predetermine and standardize the bacteriocidal potency as well as the antitoxin content after standardization becomes more rigid the product will probably be very expensive and perhaps not generally available. It does seem to be the answer at the moment until an antitoxin more completely developed with antibacteriocidal potency is commercially available. Until then the management of the scarlet fever patient must come under the following regime.

The patient should be isolated and put to bed with the advent of the prodromes. Since this should be routine in all cases of sore throat and fever or undiagnosed acute illness in childhood it is not necessary to wait for definite evidences of

scarlet fever. The isolation should be complete from the very beginning until the patient is released from quarantine. The room should be light and airy with a good heating system. Bathroom facilities for the exclusive use of patient and attendant should be included in the isolated area. Ample quarters for the nurse should be provided since she cannot leave the isolated area until the expiration of quarantine.

Dishes for the patient and nurse should never leave the suite. Garbage should be wrapped and deposited in an otherwise uncontaminated receptacle and removed directly for immediate incineration. All fomites before being sent to a laundry or dry cleaner should be soaked in antiseptics.

Upon termination of quarantine the patient should be given a bath, sent out of the isolated area, and clothed. The nurse then should wipe all walls, floors, and furniture with antiseptic solutions, including mattresses, which should then be exposed to the sun in the open air. The nurse should then take her cleansing bath and don clean clothing outside the restricted area. Toys and books should be destroyed along with the garbage at the last incineration. Lysol, chlorine, and alcohol should be supplied to the nurse freely for use throughout the quarantine. None but the gowned physician should have entrance to the isolated area. If this isolation cannot be attained the patient should be transferred immediately upon making the diagnosis to a contagious disease hospital.

With the patient in bed the diagnosis should be made as soon as possible and the treatment begun. Convalescent serum should be given if available and particularly sought if the case is a severe one. Medicine is usually unimportant. Some physicians use potassium citrate routinely but in excess this may act as a renal irritant. In some cases caffeine is needed as a stimulant and occasionally digitalis is indicated.

The nose should be kept clean with swabs, but oily or aqueous drops and sprays are contraindicated. Their use invariably means an increase in otitic complications. I have never seen any good come from local treatment of the throat and have seen much discomfort accompany and follow its use.

The employment of antiseptics in this procedure is as useless as a cobweb on a levee to hold back a flood. An ice-collar is a source of very welcome comfort for the distressed throat and in cervical adenitis. Be sure that it fits, for the ice-bag will only rest on the chin and chest and by some curious perversion invariably avoid contact with the throat and neck.

The itching can be allayed with carbolated vaselin. Purges and laxatives should never be used since they dehydrate without benefit to the patient. A cleansing enema or colonic irrigation is valuable especially if the temperature is high. Normal salt solution or bicarbonate of soda should be used. Soap enemas should never be given. The diet should include from the very beginning water for its hydrating and diuretic effect. Milk, cooked cereal, and stewed fruit must be given even in the acute stage. Baked potatoes, gelatin and junket, and orange juice within reason can augment this diet. When the fever subsides a full child's diet may be started including meat and eggs. The formerly practiced restriction in diet has no scientific background and clinically the more liberal diet has proved the better course of procedure.

An uncomplicated case should be kept in bed three weeks following the subsidence of the temperature. The urine should be examined two or three times weekly and in complicated cases daily.

The management of complications must be all too frequently surgical. For example, middle ear disease indicates free incision of the drum if this membrane is reddened or glazed. In dealing with the *Streptococcus hemolyticus* one should not wait for bulging since spontaneous rupture of the drum or procrastination in its incision is followed by an unnecessarily high percentage of mastoid infections. If a mastoiditis develops scrupulous cleaning out of all cells and the tip is necessary. If the lateral sinus is involved even if no clot has formed therein it should be removed. In the event that it is not, bacteremia will follow to place the patient in further jeopardy. Mere puncture of the mastoid antrum sim-

ply begs the question and offers another sacrifice to the surgical approach.

In cases of blood stream infection and in cases of severe toxemia frequent small blood transfusions may be given from donors who are comparatively recent scarlet fever convalescents. These act with the same favorable results generally speaking as other types of immunotransfusions. Transfusions in scarlet fever have not been given the emphasis that they justly deserve and many of the severer cases would be better treated with them than with antitoxin.

Arthritis should be treated by immobilization and soothing wet dressings. The surgical complications could be discussed better by a surgeon of experience. Carditis should be managed according to the same indications as in its occurrence in other diseases.

A little more detail in the discussion of renal complications is in order. Vomiting and fever most frequently usher in nephritis. Lethargy or delirium, convulsions or coma, may occur. Anuria may occur and persist for several days. When the child begins to void after such a period large amounts of blood are passed. In other cases the urine will contain much albumin, blood, granular and hyaline casts. Edema is apt to occur in the latter type. The blood pressure and blood chemistry may be undisturbed and if they are disturbed it is only for a brief period of time. Complete recovery does take place in a large number of these cases.

In the last few years there have been many changes in the manner of treatment. Irritants and alkalis had best be avoided. Diuretics should not be employed in the case of anuria or in a case in which the output is very low, at least until there is an obvious trend upward in the urine output. Caffeine and theobromine-sodium salicylate are the best of the diuretics although ammonium chloride should also be regarded with favor. Temporary use of a salt-poor diet is indicated in the presence of edema. It is impossible to give a salt-free diet. Protein should be given in amounts equal to the body demands. Even larger quantities should be given if the

albumin output is very large. It is obvious then that a liberal diet should be used. Fluid intake should not be restricted.

Bleeding may be indicated followed by the transfusion of smaller quantities of blood than were removed. Careful watch must be kept on the acid-base balance and the blood serum protein. Prognostically the renal functional tests have not proved their value, at least in children. In the presence of edema and high blood pressure the intravenous use of magnesium sulphate after the technic of Blackfan and McKhann is effectual.

Hot packs are helpful and the fears expressed in their use by some are groundless. During convalescence and in some cases even before iron tonics are signally helpful. Varying the type of iron frequently seems to add to the value of this mineral.

Until recently little or no attention has been paid to the most frequent of scarlet fever complications, that is, sinusitis. The routine use of nasal douches, sprays, and applications, while not consciously employed for sinus disease, impaired drainage and spread infection rather than abetted the recovery from this persistent complication. Drainage is the important clue to the correction of sinusitis. It can best be accomplished by keeping the nares open and as free as possible of discharges and edematous membranes. Aqueous applications can be used for this purpose and never drops or sprays. Surgical interference is never indicated. Mild suction also aids in the drainage. x-Ray treatments can be used in the persistent or chronic cases.

When desquamation begins it has been the custom to give cocoa butter rubs which are comforting and may aid in the removal of the peeling skin.

A patient presented for release from quarantine to be eligible for contact with his fellows must be examined physically and passed upon on the following counts. There must be no suppurative discharge from any part of the body. There must be no nasal discharge or moisture. Since sinusitis may not show itself before the third week this second postulate can-



not be answered before the fourth week. The hidebound rule of health departments and some others interested in this problem that desquamation must be complete before release from quarantine shall take place has its only working hypothesis in the fact that it measures in many cases the period in which the two preceding postulates are apt to be operative. Since the desquamation is noninfectious and all of the cases of completed desquamation cannot meet the postulates it is obviously an unscientific and inaccurate criterion in the long run. Incidentally two weeks after the completion of desquamation a secondary desquamation of the hands and feet may occur. This is of no significance whatever but complicates the desquamation criterion for release from quarantine.

It is obvious that the discharge from a mastoid, a running ear, or other open wound would deceive no one as a source of "return" cases. The persistent sinusitis with its irregular discharge and its sometimes trivial residual nasal moisture is frequently overlooked or ignored and it is from these cases that the disease is spread even many months after they have been forgotten as potential carriers. For many obvious reasons cultures are impractical as a check on these cases.

Scarlet fever today needs six cardinal points of attack. First, a more comprehensive and intimate knowledge of the clinical aspects of the disease. Second, a more complete isolation of patients. Third, longer periods of confinement to bed and a more liberal view of the management of the patient's diet. Fourth, a more modern and radical approach to the complications, particularly the surgical. Fifth, a more careful and more reasonable approach to the problem of release from quarantine. Sixth, the liberation from the shackles of commercialism of the bacteriological and serological studies necessary for the evolution of a true prophylaxis and specific cure for this disease. It is not one man's God given field for exclusive study and every bacteriologist and serologist should be permitted to study the problems after a return to our original ethics as a basis.

## CLINIC OF DR. MARTIN J. SOKOLOFF

JEFFERSON MEDICAL COLLEGE

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### TREATMENT OF ACUTE PLEURISY IN GENERAL PRACTICE

AN attack of acute pleurisy should always be given careful consideration, since even in its mildest form it may be an indication of serious disease in the underlying lung or elsewhere in the body. Not infrequently such an attack directs attention to pathological change in other organs, which for a time at least might have otherwise escaped detection. Failure to study and manage properly an apparently trivial pleurisy may have an important bearing upon the future health of the patient.

#### ETIOLOGY

Acute inflammation of the pleura may be either primary or secondary. The primary form is rare. It occasionally results from exposure to cold or from injury to the chest wall. The majority of cases of primary pleurisy are tuberculous and constitute the group formerly classified as idiopathic pleurisy. Funk was of the opinion that the tubercle bacillus is the probable etiological factor in 90 per cent of cases of primary pleurisy. Frequently a case which is apparently primary is in reality secondary to a tuberculous tracheobronchial lymph gland, or to a subpleural tuberculous focus in the lung too small to be recognized either clinically or roentgenographically. Every case of pleurisy for which no definite cause can be found should be regarded as tuberculous in origin. On the other hand, evidence of pleural inflammation is often the first manifestation of pulmonary tuberculosis and it may precede the appearance of frank pulmonary symptoms by many months.

The secondary form is a result of extension of infection from some obvious focus elsewhere. It occurs in association with such pulmonary diseases as tuberculosis, lobar pneumonia, bronchopneumonia, abscess, bronchiectasis, gangrene, infarction, the mycotic infections or neoplasm. Infections may spread to the pleura from inflammatory processes involving the pericardium, the endocardium, the mediastinum or from organs below the diaphragm. It may follow infection in other parts of the body—postoperative septic infections, tonsillitis, or nephritis. Occasionally it occurs in rheumatic fever as part of a general involvement of the serous membranes.

#### CLINICAL VARIETIES

Acute pleurisy is best classified clinically according to the type of exudate present. It may be fibrinous or plastic (dry), serous or serofibrinous (pleurisy with effusion), suppurative (empyema) or hemorrhagic.

Inflammation of the pleura results first in the formation of a fibrinous exudate. In a typical attack of dry pleurisy the exudate remains fibrinous throughout. If the inflammation progresses, the amount of serous exudate may exceed the amount of fibrin, resulting in serofibrinous pleurisy. The suppurative form is the result of infection by pneumococci, streptococci or other pyogenic organisms, and occasionally by tubercle bacilli. Hemorrhagic pleurisy may occur as a complication of pneumonia but it is usually the result of tuberculosis or of malignant disease of the pleura.

#### TREATMENT

Since inflammation of the pleura is frequently an accompaniment of, or an extension from, an infectious process elsewhere, it is obvious that a rational system of management of this condition must take into consideration the underlying and associated pathological conditions. Detailed consideration of these factors would lead this discussion too far afield, therefore, I shall limit my remarks to the relief of the pleurisy itself

and briefly summarize the principles to be applied during and after the acute attack.

The management of acute pleurisy is peculiarly a problem for the general practitioner. Since the clinical course is of relatively short duration and alleviation of annoying symptoms can usually be promptly obtained, the majority of patients with acute pleurisy can be satisfactorily treated at home. Hospitalization is required only when thorough study is necessary to determine the exact etiology or when major surgical procedures are indicated.

**Dry Pleurisy.**—Regardless of the mildness of the symptoms, rest in bed is essential. The patient should remain in bed until after the pain and fever have subsided. The diet should be nourishing and easily digestible. In the beginning a saline purge is indicated and afterward daily evacuation of the bowels should be assured.

The most important consideration in the treatment of dry pleurisy is the relief of pain. If the pain is not severe it may be relieved by counterirritation in the form of mustard plasters or local application of tincture of iodine. Mustard plasters are ideal counterirritants. They can be readily prepared, their strength can be regulated to suit the age of the patient and sensitivity of the skin, and the degree of rubefaction produced by them can be easily controlled. They are especially useful in the mild recurring attacks of pleurisy in tuberculous patients.

If the pain is severe, immobilization of the affected side by adhesive plaster usually affords immediate relief. With the chest in the position of full expiration, strips of plaster about  $2\frac{1}{2}$  inches wide are applied. The strips are started across the vertebral column, drawn tightly around the affected side and attached just beyond the midline in front. They should be placed at right angles to the vertebral column and not follow the line of the ribs. Each strip should overlap the preceding one by one third its width. If the pain is localized in the lower part of the chest two or three strips will suffice, but if it is widely distributed, the strips should be applied up

to the axilla. Hairy chests should be shaved before the adhesive plaster is applied in order to facilitate its removal. In the female, the breast should be drawn up and a small pad of cotton placed over the nipple before being covered by the adhesive. If the pain is in the upper part of the chest several strips may be attached to the anterior chest wall at the level of the fourth rib and pulled firmly over the shoulder to below the spine of the scapula. The plaster should be removed after four or five days or sooner if the patient complains of itching.

If the strapping does not afford complete relief from pain, codeine sulphate may be given by mouth in  $\frac{1}{4}$ -grain doses every three or four hours. The codeine will also control the annoying cough which is sometimes present. Acetylsalicylic acid, 5 grains, may be combined with codeine in capsule form. In severe pain not relieved by the above measures, morphine,  $\frac{1}{4}$  grain, may be administered hypodermically, but this is rarely necessary.

**Pleurisy with Effusion.**—The fundamental rules regarding rest, diet, elimination and pain described for dry pleurisy are to be followed. Rest in bed should be continued until the fluid has entirely disappeared. Pain is not an important consideration in this variety of pleurisy, as it is present only for a short time at the onset and disappears with the development of the fluid.

The most important factor in serofibrinous pleurisy is the management of the fluid. It must be borne in mind that spontaneous absorption of pleural effusion occurs frequently. Nearly all small effusions, and occasionally large ones, disappear if the patient is at rest in bed. If the general condition is good and if dyspnea and fever are not causing concern, it is advisable to continue bed rest for several weeks in the hope that spontaneous absorption will take place.

A salt-free diet, restriction of fluid intake, the application of cups or fly blisters to the chest wall, and the induction of profuse diuresis by means of such drugs as theobromine sodium salicylate and salyrgan, have been advised to increase

absorption of the fluid. These measures are of doubtful value, and, as a rule, only add to the discomfort of the patient.

If the effusion occurs as a complication of rheumatic fever salicylates are beneficial. Sodium salicylate, 20 grains, combined with an equal quantity of sodium bicarbonate may be given every three or four hours.

Calcium is believed by some to favor the absorption of fluid from the pleural cavity. Calcium chloride (20 grains) or calcium gluconate (60 grains) may be given orally every three or four hours, or 5 or 10 cc. of a 10 per cent solution of calcium gluconate may be given intravenously once or twice daily for four days. If given intravenously, calcium should be injected slowly in order to avoid unpleasant subjective sensations. According to Kreich, effusions occurring as complications of pneumothorax therapy in tuberculosis may disappear following the intrapleural injection of calcium. He advises the removal of 5 or 10 cc. of the pleural fluid and its replacement by a similar amount of 10 per cent solution of calcium gluconate once daily for three or four days.

Thoracentesis or aspiration of fluid from the pleural cavity is indicated as follows:

1. For diagnostic purposes (15 to 20 cc. is sufficient for cytodiagnosis, culture and animal inoculation).
2. If the effusion is causing cyanosis or dyspnea.
3. If there is continued fever.
4. If the effusion is increasing in amount.
5. If there is no absorption after a reasonable period of conservative treatment (bed rest).
6. If tubercle bacilli are present in the sputum and the opposite lung appears normal the effusion should be converted into a therapeutic pneumothorax by gradual replacement with air.

While aspiration of fluid from the pleural cavity is a relatively safe procedure, it is not entirely without danger. The fluid must be removed slowly and not more than 1500 cc. should be withdrawn at one time. Rapid diminution in intrapleural pressure may cause sudden shifting of mediastinal

structures with immediate production of alarming symptoms. The complications of thoracentesis are: (1) severe cough, (2) pain, (3) fainting or dizziness, (4) dyspnea, (5) hemoptysis, (6) pulmonary edema and (7) pleural shock resulting in sudden death. If the patient coughs or complains of pain or dizziness during thoracentesis, the operation should be stopped and no other attempts to remove the fluid should be made until at least twenty-four hours have elapsed.

*Technic of Thoracentesis.*—The patient should lie on the sound side, close to the edge of the bed, with the arm extended over the head. A firm pillow should be placed under the lower part of the chest to arch the affected side thus increasing the width of the intercostal spaces. The operation must be performed under rigidly aseptic precautions. Puncture should be made through the sixth or seventh interspace, usually just in front of the angle of the scapula. The skin in the area selected is painted with tincture of iodine and the excess iodine removed with alcohol. Local anesthesia is necessary and a 2 per cent procaine solution may be used for this purpose, being injected intracutaneously by means of a fine hypodermic needle until a wheal is formed. The needle should then be withdrawn and a 20-gauge 3-inch needle attached to the syringe. This needle is inserted through the bleb and is gently forced into the deeper tissues as constant pressure is made on the piston of the syringe. Puncture should be made close to the upper border of the rib in order to avoid injury to the intercostal vessels. The parietal pleura should be carefully injected because of its high degree of sensitivity. Sudden lessening of resistance will indicate that the parietal pleura has been penetrated and that the needle is in the pleural cavity. If traction is made on the piston, the fluid can be seen to rise in the glass tip and enter the barrel of the syringe. The needle should never be introduced up to the hilt for if it breaks at this point it will be difficult to recover. If the fluid is required for diagnostic purposes only, the small syringe is replaced by a 20 cc. syringe and the required amount of fluid is withdrawn and transferred to a sterile container.

If aspiration is to be performed one of the following methods is used:

1. *Negative Pressure Aspiration*.—The Potain aspirator is the apparatus most frequently used in this procedure. It consists of a bottle fitted with a two-way stopcock. One opening is connected to a vacuum hand pump by a piece of rubber tubing. The other opening is connected to the needle in the chest by a similar piece of tubing. The air is removed from the bottle by means of the pump and the valve between the bottle and the pump is closed. The other valve is then opened and the fluid flows from the pleural cavity into the bottle because of the difference in pressure. This apparatus should always be tested before using to make sure there is no leak in the valve and no block in the tubing.

2. *Siphonage*.—This is a simple method of removing fluid from the pleural cavity but it should be used only if an aspirator is not available. A rubber tube is attached to the needle in the chest and the free end is put into a basin half filled with water, which is placed on the floor. A cough will start the flow of fluid through the tube and it will be drawn into the basin by siphonage.

3. *Air Replacement*.—This is indicated in cases of pulmonary tuberculosis where continued collapse of the lung is desired. The effusion is converted into an artificial pneumothorax by removing the fluid and replacing it with air. Two punctures should be made for this purpose, one above the other, in different interspaces. The fluid should be removed through the lower puncture and air introduced through the upper. A pneumothorax apparatus should be used for the introduction of the air so that the amount of air entering the pleural cavity can be measured and the pressure controlled. The fluid should not be entirely removed at one operation, the replacement being accomplished gradually.

After aspiration has been completed the needle should be withdrawn and the puncture point sealed with cotton soaked in collodion or held in place by adhesive.

**Empyema**.—The presence of an acute purulent pleural



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**Empyema**.—The presence of an acute purulent pleural

effusion is an indication for immediate drainage of the pleural cavity. In rare instances, however, repeated aspiration of the exudate may cause reabsorption. Resolution of purulent exudates has been noted by Major following the injection of gentian violet into the pleural cavity. He recommends aspiration of the fluid and the introduction of 100 cc. of a 1:5000 aqueous solution of gentian violet. In the majority of cases intercostal incision or rib resection and drainage is necessary.

**Hemorrhagic Pleurisy.**—In the absence of infection hemorrhagic pleural effusions will usually be absorbed spontaneously. Massive effusions, or those which are causing fever or dyspnea, should be aspirated. In the presence of infection, prompt surgical treatment to establish free drainage is indicated.

#### AFTER-TREATMENT

Because acute inflammation of the pleura is so often the result of tuberculous infection, the after-treatment, in many instances, is more important than the treatment of the acute attack. All patients who have had more than one attack of dry pleurisy, or who have developed pleural effusion for which no cause can be found, should be considered tuberculous. A routine method of living, with special reference to rest, diet and fresh air should be outlined and the importance of adhering to this régime carefully explained. If the general condition is unfavorable or convalescence is slow, sanatorium treatment is advisable. Following an acute attack of pleurisy the patient should be reexamined at regular intervals, over a period of several years, for evidence of pulmonary disease. After empyema or hemorrhagic pleurisy the ordinary procedures advised during convalescence from any severe infection must be followed.

# CUMULATIVE INDEX

- ABDOMINAL diseases causing fever in children, *July*, 21  
 Abortion, diagnostic mistakes, *July*, 76  
     habitual, *July*, 81, 93  
 Abscess, abdominal, in children, *July*, 26  
     mediastinal, in children, *July*, 18  
     of brain in children, *July*, 43  
     of kidney, multiple, in children, *July*, 33  
     of lung, multiple, in children, *July*, 18  
     perinephric, in children, *July*, 33  
     retropharyngeal, in children, *July*, 13  
     subphrenic, in children, *July*, 26  
 Adenoids, infected, fever due to, *July*, 10  
 Alternation of heart, *July*, 188  
 Amebic dysentery in children, *July*, 24  
 Anemia, sickle cell, *July*, 55  
 Appendicitis, acute, in aged, *July*, 133  
     in children, fever in, *July*, 25  
 Arcus senilis, *July*, 128  
 Arrhythmias, cardiac, diagnosis and treatment, *July*, 175  
 Arteriosclerosis in cardiovascular-renal disease, *July*, 209  
 Arthritis, gonorrheal, in male, *July*, 152  
 Asphyxia neonatorum, *July*, 99  
 Aspiration in pleurisy, *July*, 329  
 Associated movements, automatic, abnormal, *July*, 227  
 Atelectasis, pulmonary, in newborn, *July*, 106, 111  
 Auricular fibrillation, *July*, 181  
     flutter, *July*, 184  
 Autohemotherapy in herpes zoster, *July*, 245  
  
 BLEPHAROSPASM in parkinsonism, *July*, 228  
 Blood, disorders, genetic aspects, *July*, 253  
     iodine, in hyperthyroidism, *July*, 286  
 Bones, diseases, in aged, *July*, 138  
 Botulism, *July*, 265  
     in children, *July*, 28  
  
 Brain abscess in children, *July*, 43  
     tumors in children, *July*, 47  
 Brill's disease, *July*, 52  
 Bronchiectasis as cause of fever in children, *July*, 18  
 Bronchitis, chronic, in aged, *July*, 135  
 Brucella melitensis, *July*, 51  
  
 CARBUNCLE of kidney in children, *July*, 33  
 Carcinoma of cervix, diagnostic mistakes in, *July*, 78  
 Cardiac. See *Heart*.  
 Cardiovascular disease in aged, *July*, 139  
     physical exercise in, *July*, 191  
 Cardiovascular-renal disease, preventive aspects, *July*, 209  
 Cerebral edema and hemorrhage in newborn, *July*, 105, 109  
 Cervical lymphadenitis in children, *July*, 14  
 Cervix, carcinoma of, diagnostic mistakes, *July*, 78  
 Cogwheel motor rigidity, *July*, 232  
 Colds, common, as cause of fever in children, *July*, 9  
 Colitis, ulcerative, in children, *July*, 24  
 Contractions of heart, premature, *July*, 177  
 Corpus spongiosum, marked induration, in gonorrhea, *July*, 155  
 Cowperitis, gonorrheal, *July*, 155  
 Cyanosis of newborn, diagnosis and treatment, *July*, 99  
 Cystitis in children, *July*, 34  
  
 DEHYDRATION fever in children, *July*, 47  
 Diabetes mellitus with hypothyroidism, *July*, 279  
 Diaphragmatic pleurisy in children, *July*, 18  
 Dick antitoxin, *July*, 314  
     test, *July*, 312  
     toxin, *July*, 313  
 Diet in cardiovascular-renal disease, *July*, 214

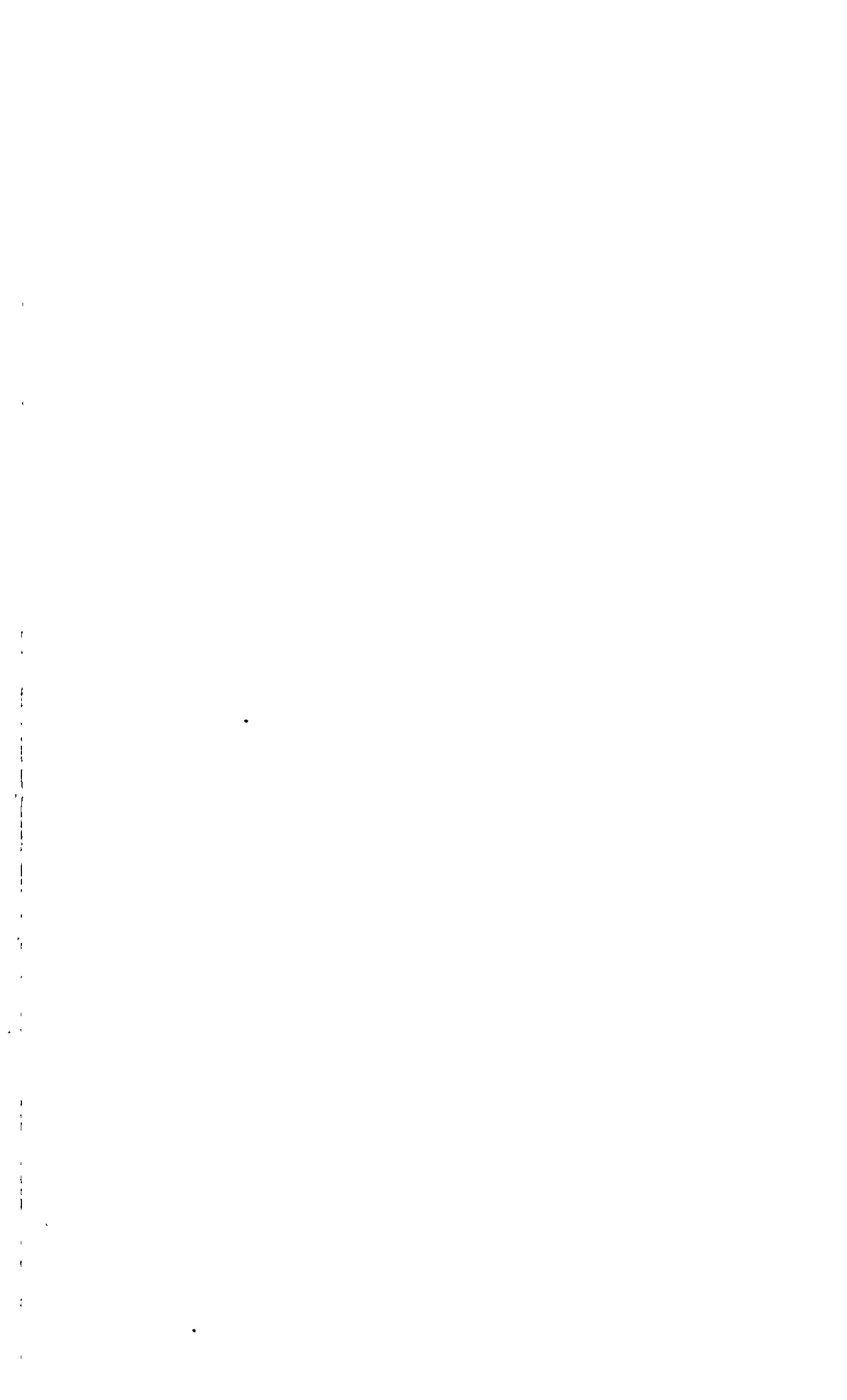
- Digestive tract diseases in aged, *July*, 132
- Diverticula, esophageal, in aged, *July*, 132
- Drugs causing fever in children, *July*, 45
- Dysentery, amebic, in children, *July*, 24
- bacillary, in children, *July*, 24
- Dyspituitarism, postencephalitic, *July*, 229
- Dystonia, neurovegetative, *July*, 233
- ECTOPIC pregnancy, *July*, 77
- Edema, cerebral, in newborn, *July*, 105, 109
- Empyema, *July*, 329
- encapsulated, in children, *July*, 18
- Encephalitis, epidemic, dyspituitarism following, *July*, 229
- parkinsonism following, diagnosis and treatment, *July*, 223
- in children, *July*, 39
- Endocarditis, subacute bacterial, in children, *July*, 57
- Endocervicitis, chronic, treatment, *July*, 119
- Endocrine glands, disease of, in aged, *July*, 138
- Epididymitis, gonorrheal, *July*, 150
- Erysipelas in aged, *July*, 137
- Esophagus, pressure diverticula, in aged, *July*, 132
- Exanthem subitum, *July*, 48
- Exercise, physical, in cardiac conditions, *July*, 191
- Exophthalmic goiter, *July*, 285
- Extrasystoles, *July*, 177
- FEVERS in childhood, obscure origin, symposium on, *July*, 1
- Folliculitis, gonorrheal, *July*, 153
- Food poisoning in children, *July*, 27
- Fractures in aged, *July*, 138
- GALLSTONES in aged, *July*, 134
- Genetic aspects of certain blood-system disorders, *July*, 253
- Genito-urinary system, diseases, in aged, *July*, 134
- Geriatrics, *July*, 127
- Glandular fever in children, *July*, 55
- Goiter, toxic, *July*, 285
- Gonorrhea in male, complications, treatment, *July*, 147
- Gonorrheal arthritis, *July*, 152
- prostatitis, *July*, 150, 161
- vulvovaginitis in adults, *July*, 123
- in children, 123
- Graves' disease, *July*, 285
- Grippe, intestinal, *July*, 26
- Gynecology, diagnostic mistakes, *July*, 75
- problems of family physician, symposium on, *July*, 59
- HEART, alternation of, *July*, 188
- block, *July*, 185
- disease, in aged, *July*, 139
- physical exercise in, *July*, 191
- with cyanosis in newborn, *July*, 105, 111
- irregularities, diagnosis and treatment, *July*, 175
- premature contractions, *July*, 177
- Hemoglobinuria, paroxysmal, *July*, 56
- Hemophilia, *July*, 258
- Hemorrhage, cerebral, in newborn, *July*, 105, 109
- Herpes zoster, treatment, *July*, 239
- Hodgkin's disease in children, *July*, 54
- Hormone therapy in habitual abortion, *July*, 96
- in sterility, *July*, 70
- Hypertension in cardiovascular-renal disease, *July*, 209
- Hyperthyroidism, *July*, 285
- Hypogonadism, primary, *July*, 68
- Hypothyroidism in diabetes mellitus, *July*, 279
- ICTERO-ANEMIA, hemolytic, genetic aspects, *July*, 256
- Impedance angle in hyperthyroidism, *July*, 287
- Infections, acute, in aged, *July*, 137
- Inflammatory disease, pelvic, ectopic pregnancy and, differentiation, *July*, 77
- Influenza in children, fever in, *July*, 18
- Inguinal lymphadenitis in gonorrhea in male, *July*, 156
- Intestinal grippe, *July*, 26
- obstruction in aged, *July*, 133
- tuberculosis in children, *July*, 21
- Iodine, blood, in hyperthyroidism, *July*, 286
- JAUNDICE, epidemic, in children, *July*, 29
- KIDNEY, abscesses, multiple, in children, *July*, 33
- carbuncle, in children, *July*, 33
- tuberculosis, in children, *July*, 34
- tumors, in children, *July*, 34

- LEUKEMIA in children, *July*, 54  
 Liver, enlargement, diseases associated with, diagnosis, *July*, 295  
 Lung, abscesses, multiple, in children, *July*, 18  
     diseases, in aged, *July*, 135  
 Lymph nodes, mesenteric, tuberculosis of, *July*, 22  
 Lymphadenitis, cervical, as cause of fever in children, *July*, 14  
     inguinal, in gonorrhea in male, *July*, 156  
 Lymphangitis, gonorrheal, in male, *July*, 156
- MALARIA in children, *July*, 53  
     inoculata, *July*, 53  
 Malpositions of uterus, diagnostic mistakes, *July*, 79  
 Malta fever, *July*, 51  
 Mastoiditis as cause of fever, *July*, 15  
 Mediastinal abscess in children, *July*, 18  
     infection, as cause of fever in children, *July*, 18  
 Meningitis, acute aseptic, *July*, 41  
     lymphocytic, *July*, 40  
     meningococcal, *July*, 35  
     miscellaneous forms, *July*, 38  
     syphilitic, *July*, 42  
     tuberculous, *July*, 37  
 Menopause, abnormal bleeding before and after, causes, *July*, 83  
 Mesenteric lymph nodes, tuberculosis, *July*, 22  
 Metabolism, basal, in hyperthyroidism, *July*, 288  
 Miscarriage, diagnostic mistakes in, *July*, 76  
     persistent, *July*, 81  
 Monckeberg's sclerosis, *July*, 130  
 Mononucleosis, acute infectious, *July*, 55  
 Morbus coeruleus, *July*, 106
- NEOARSPHENAMINE in herpes zoster, *July*, 248  
 Nephrosclerosis in aged, *July*, 134  
 Newborn, cyanosis of, *July*, 99  
     sepsis of, *July*, 47
- OBSTETRIC problems of family physician, symposium on, *July*, 59  
 Oculogyric crises, *July*, 228  
 Oertel terrain exercises, *July*, 203  
 Old age, diseases of, *July*, 127, 131  
 Ornstein's triad, *July*, 234  
 Osteomyelitis in children, *July*, 49  
 Otitis media, fever due to, *July*, 15  
 Ovalocytosis, *July*, 257  
 Ovarian failure, primary, *July*, 68
- PAGET's disease in aged, *July*, 138  
 Pancreatitis, acute, in children, *July*, 26  
 Parafrenal sinusitis in gonorrhea, *July*, 158  
 Paraphimosis, gonorrheal, *July*, 157  
 Paratyphoid fever in children, *July*, 23  
 Parkinsonism, incipient, diagnosis and treatment, *July*, 223  
 Parrot fever, *July*, 56  
 Pastia's sign, *July*, 309  
 Pel-Ebstein Hodgkin's disease, *July*, 54  
 Pelvic inflammatory disease, ectopic pregnancy and, differentiation, *July*, 77  
 Perinephric abscess in children, *July*, 33  
 Peritonitis in children, fever in, *July*, 25  
     tuberculous, in children, *July*, 22  
 Phimosis, inflammatory, in gonorrhea, *July*, 156  
 Phlebitis, dorsal, gonorrheal, *July*, 156  
 Phrenic nerve injury in newborn, *July*, 105, 110  
 Physical exercise in cardiac conditions, *July*, 191  
 Pill-rolling tremor, *July*, 232  
 Pituitary deficiency in sterility, *July*, 67  
 Pituitrin in herpes zoster, *July*, 246  
 Pleurisy, acute, *July*, 323  
     diaphragmatic, in children, *July*, 18  
     dry, *July*, 325  
     hemorrhagic, *July*, 330  
     with effusion, *July*, 326  
 Pneumonia in aged, *July*, 136  
     in children, fever in, *July*, 17  
 Poliomyelitis, *July*, 38  
 Postmenopausal bleeding, causes, *July*, 88  
 Pregnancy and hypertension, *July*, 221  
     ectopic, pelvic inflammatory disease and, differentiation, *July*, 77  
 Premenopausal bleeding, causes, *July*, 85  
 Prostatic hypertrophy, *July*, 135  
 Prostatitis, chronic, management, *July*, 161  
     foci of infection in, *July*, 168  
     gonorrheal, *July*, 150, 161  
 Psittacosis, *July*, 56  
 Psychoses in aged, *July*, 140  
 Pulsus alternans, *July*, 188

- Purpura in children, *July*, 57  
 Pyelitis in children, fever due to, *July*, 31  
 Pyuria in children, fever due to, *July*, 31  
  
 RAT-BITI fever, *July*, 52  
 Relapsing fever, *July*, 53  
 Renal cardiovascular disease, preventive aspects, *July*, 209  
 Respiratory disorders in parkinsonism, *July*, 229  
     infections, lower, in children, fever due to, *July*, 17  
     upper, in children, fever due to, *July*, 9  
 Retropharyngeal abscess as cause of fever in children, *July*, 13  
 Rheumatic fever in children, *July*, 27, 50  
 Riedel's lobe, *July*, 299  
 Rocky Mountain spotted fever, *July*, 52  
 Roentgen treatment of herpes zoster, *July*, 244  
 Roseola infantum, *July*, 48  
 Rumpel-Leede's sign, *July*, 309  
  
 SCARLET fever, *July*, 307  
 Schultz-Charlton reaction, *July*, 315  
 Sclerosis, Monckeberg's, *July*, 130  
 Scurvy in children, *July*, 49  
 Seminal vesiculitis in gonorrhea, *July*, 154  
 Senescence, changes of, *July*, 128  
 Sepsis of newborn, *July*, 47  
 Sicklemia, *July*, 55  
     genetic aspects, *July*, 258  
 Sinus infection, paranasal, fever due to, *July*, 11  
 Sinusitis, parafrenal, in gonorrhea, *July*, 158  
 Sodium iodide in herpes zoster, *July*, 247  
 Spherocytes, *July*, 256  
 Splenomegaly, diseases associated with, diagnosis, *July*, 295  
 Sterility in female, *July*, 63  
     in male, *July*, 61  
 Stokes-Oertel terrain exercises, *July*, 203  
 Subphrenic abscess in children, *July*, 26  
 Syphilitic meningitis in children, *July*, 42  
  
 TACHYCARDIA, paroxysmal, simple, *July*, 179  
 Teeth, abscessed, in children, *July*, 48  
 Teething, fever due to, *July*, 48  
 Telangiectasia, hereditary hemorrhagic, *July*, 257  
 Tetany in newborn, *July*, 112  
 Thoracentesis in pleurisy, *July*, 328  
 Thymus enlargement in newborn, *July*, 107, 111  
 Tonsils, infected, and fever, *July*, 10  
 Tremor, pill-rolling, *July*, 232  
 Trichomonas vaginalis vaginitis, treatment, *July*, 125  
 Tuberculosis, intestinal, in children, *July*, 21  
     of kidney in children, *July*, 34  
     of mesenteric lymph nodes, *July*, 22  
     pulmonary, in aged, *July*, 136  
     in children, *July*, 19  
 Tuberculous meningitis in children, *July*, 37  
     peritonitis in children, *July*, 22  
 Tularemia, *July*, 51  
 Tumors of brain in children, *July*, 46  
     of kidney in children, *July*, 34  
 Typhoid fever in children, *July*, 23  
 Typhus fever, *July*, 52  
  
 UNDULANT fever in children, *July*, 51  
 Urethritis, gonorrheal, in male, *July*, 147  
 Uterus, malpositions, diagnostic mistakes, *July*, 79  
  
 VAGINAL bleeding, abnormal, pre- and postmenopausal, causes, *July*, 83  
     discharges, diagnosing, *July*, 80  
 Vascular disease, hypertensive, *July*, 209  
 Vesiculitis, seminal, in gonorrhea, *July*, 154  
 Vulvovaginitis, different types, treatment, *July*, 122  
  
 WEIL's disease, *July*, 29  
  
 YEAST vulvovaginitis, treatment, *July*, 124  
  
 ZOSTER ophthalmicus, *July*, 240  
     oticus, *July*, 240







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# CONTENTS

	PAGE
ENDOCRINE SYMPOSIUM	335
Borderline Endocrine Disturbances	337
By DR. CYRIL M. MACBRYDE	
The Diagnosis and Treatment of Endocrine Infantilism	353
By DR. MAX DEUTCH	
Endocrine Obesity	369
By DR. HAROLD A. BUTLER	
The Treatment of Pituitary Insufficiency and Pituitary Hyperfunction	379
By DRS. DAVID P. BARR and KURT MANSBACHER	
Diagnosis and Treatment of Hyperinsulinism	393
By DR. LOUIS F. AHELEN	
Encephalitis: Clinical Types, Their Symptoms, Diagnosis and Treatment	415
By DR. THEODORE C. HEMPELMANN	
The Early Diagnosis and Treatment of Emphysema	439
By DR. H. L. ALEXANDER	
Constipation: The Laxative Value of Bulky Foods	449
By DRS. WILLIAM H. OLMSTED, RAY D. WILLIAMS and THEODORE BAUERLEIN	
Peptic Ulcer	461
By DR. JOSEPH W. LARIMORE	
The Diagnosis of the Stoneless Gallbladder	471
By DR. WENDELL G. SCOTT	
Diagnosis and Treatment of Pulmonary Bleeding	483
By DR. ALFRED GOLDMAN	
The Diagnosis and Prevention of Silicosis (The Silicosis Problem)	497
By DR. J. J. SINGER	
The Classification and Treatment of Infantile Colic or Gastro-enterospasm	511
By DR. PARK J. WHITE	
The Treatment of Uremia	527
By DR. EDWARD W. CANNADY	
The Significance of Abnormal Cardiac Rhythms	537
By DR. DREW LUTEN	
Treatment of Myocardial Insufficiency	547
By DR. ARTHUR E. STRAUSS	
Neuroses and Psychoses as the General Practitioner Sees Them	559
By DR. SIDNEY I. SCHWAB	
The Diagnosis and Treatment of Functional Disorders of Children	581
By DR. P. E. KUBITSCHKE	
The Treatment of Bronchial Asthma	591
By DR. CHARLES H. EYERMANN	
Vomiting in the Newborn	615
By DR. ALEXIS F. HARTMANN	
The Differential Diagnosis of Diseases of the Breast	625
By DR. ISAAC Y. OLCH	
Eczema and Environment	651
By DRS. MARTIN F. ENGMAN, RICHARD S. WEISS and MARTIN F. ENGMAN, JR.	
The Treatment of Gonorrheal Vaginitis	665
By DR. T. K. BROWN	
Cumulative Index	679

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## ENDOCRINE SYMPOSIUM

THE following clinics are included in this Symposium:

Cyril M. MacBryde: BORDERLINE ENDOCRINE DISTURBANCES.

Max Deutch: THE DIAGNOSIS AND TREATMENT OF ENDOCRINE INFANTILISM.

Harold A. Bulger: ENDOCRINE OBESITY.

David P. Barr and Kurt Mansbacher: THE TREATMENT OF PITUITARY INSUFFICIENCY AND PITUITARY HYPERFUNCTION.

Louis F. Aitkin: DIAGNOSIS AND TREATMENT OF HYPERINSULINISM.



## CLINIC OF DR. CYRIL M. MACBRYDE

FROM THE DEPARTMENT OF MEDICINE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND THE BARNES HOSPITAL

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### BORDERLINE ENDOCRINE DISTURBANCES

THE recognition of typical examples of endocrine disease should not be difficult. The classical signs of fully developed myxedema, acromegaly or Addison's disease, for example, are so impressive that their diagnosis is almost inescapable. It is not widely appreciated, however, that the milder grades of endocrine dysfunction probably occur much more frequently than the "textbook pictures," and that the presenting symptoms may be so varied or obscure as to be quite misleading. Because of their much greater frequency, and the more satisfactory response to treatment which may be expected in these less severe or "borderline" cases, their recognition is perhaps more important than the diagnosis of the fully developed, frequently hopeless glandular diseases.

### HYPOTHYROIDISM

Many patients are seen who have metabolic rates well below the average normal, yet show no signs of clinical hypothyroidism. In the absence of symptoms or signs in such individuals, who otherwise seem perfectly healthy, thyroid medication is not indicated. Further observation is advisable, since definite indications are often slow in development. It is well in such instances to remember that our conception of the normal basal metabolic rate is based upon averages of supposedly normal persons and cannot be too strictly interpreted in its individual application. It must also be kept in



mind that undernutrition alone may cause a marked lowering of the metabolic rate. Restoration of adequate food intake is often accompanied by rapid weight gain and return of oxygen consumption to normal.

Definite hypothyroidism may, however, be manifested in more or less advanced degree without evident myxedema. Symptoms occur in great variety and may include excessive fatigue, sensitivity to cold, nervousness, irritability, constipation, vague muscular or rheumatoid pains, amenorrhea, menorrhagia or metrorrhagia, dryness and roughness of the skin, thinning and dryness of the hair, pallor and dyspnea. Mental sluggishness is by no means the rule, as nervousness and irritability may be major complaints. Mental disturbances may be evidenced by a true depression. Retarded healing of skin or mucous membrane lesions may be seen. Hypothyroid patients frequently are moderately obese, but may be thin. Anemia is present in most of the cases that have persisted for some time. The condition is frequently seen in women going through the menopause, although it may occur in young girls or older women. As is true of other thyroid disorders and typical myxedema, men are affected less frequently than women.

The following reports will illustrate the importance of discovering a lowered metabolism in such atypical cases:

**Ulcer of Nasal Septum and Hypothyroidism.**—G. H., a woman of forty-nine, had suffered with a painful ulcer of the nasal septum for seven years. She had been steadily gaining weight for several years and was moderately obese. Menses were regular. There was some fatigue and dryness but no thickening of the skin. Mentally she was quite active. Her pulse rate was 66, blood pressure 130 systolic, 70 diastolic. Blood cholesterol was 240, basal metabolism minus 22 per cent. Shortly after the institution of thyroid medication improvement in the ulcer was noted. In six months the ulcer had healed completely.

**Hypothyroidism Simulating Hyperthyroidism.**—J. D., a woman of thirty-four, complained of nervousness, palpi-

tation and a swelling in her neck, all present for some years. but becoming increasingly annoying. She had had scanty menses for five years, lasting only one day. Emotional upset, weeping spells and severe depression to the point of suggesting suicide had been increasingly evident. She was moderately obese, the skin was flushed and moist, the palpebral fissures were wide and there was slight exophthalmos. The thyroid was moderately and diffusely enlarged. There was slight tremor of the fingers. The blood pressure was 110 systolic, 70 diastolic, and the pulse rate 80. The first impression was that she had mild hyperthyroidism, but the normal pulse and normal pulse pressure made this seem unlikely. The basal metabolism was minus 16 per cent. Appropriate small doses of desiccated thyroid caused a disappearance of the depressed state, lessened the irritability, and restored the menses to normal in duration and amount.

#### **Irritability, Enuresis, Obesity and Hypothyroidism.**

—Z. F., a girl of fourteen, complained of easy fatigue, laziness, enuresis, irritability and a very rapid gain in weight. She was somewhat behind girls of her own age in school. The skin was normal. Menses were regular. Pulse was 84, blood pressure 112 systolic, 78 diastolic. Basal metabolism was minus 20 per cent. Within three months after restoration of the basal metabolism to normal, all symptoms were relieved and rapid improvement was noted in her school work. Control of her weight continued to prove difficult, however, and she is still moderately obese. She now is quite energetic and has an equable disposition.

#### **Heart Block, Fainting Attacks and Hypothyroidism.**

—Blackford and Willius<sup>1</sup> and others have reported beneficial effects from thyroid medication in Adams-Stokes syndrome and complete heart block. In myxedema the interval between auricular and ventricular contractions may be much prolonged, and the pulse very slow, but true heart block appears to be very rare.

L. M., a man aged forty-four, had weakness for a year, constipation, and frequent occipital headaches. One day

mind that undernutrition alone may cause a marked lowering of the metabolic rate. Restoration of adequate food intake is often accompanied by rapid weight gain and return of oxygen consumption to normal.

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L. M., a man aged forty-four, had weakness for a year, constipation, and frequent occipital headaches. One day

while attending church he lost consciousness for some minutes. There were no convulsive movements and upon regaining consciousness he was able to walk home. Similar attacks occurred at irregular intervals over a period of several months. He was obese and there were numerous fairly large lipomata on arms, back, abdomen and legs. The heart was not enlarged and there were no murmurs. Blood pressure was 105 systolic, 80 diastolic. The pulse rate was 36. The skin was not dry or thickened. Basal metabolism tests were minus 32 and minus 37 per cent. The electrocardiograms showed slurring of the QRS complexes, rates 36 to 54, and the P-R interval was 24 seconds. This was interpreted as evidence of delayed auriculoventricular conduction, possibly partial heart block. With 3 grains of thyroid per day the metabolism rose to normal, the pulse ranged from 64 to 78, the P-R interval was shortened, the blood pressure rose to 130 systolic, 70 diastolic, and there was no recurrence of the fainting attacks.

The relief of the attacks following the restoration of the metabolism to normal suggested that the syncope might have been associated with the low blood pressure and prolonged P-R interval resulting from the hypothyroidism.

**Anemia, Constipation, Muscular Pains, Cramps and Hypothyroidism.**—D. R., a woman aged forty-nine, had noticed easy fatigue for four months. Constipation had been severe and had been controlled only by generous use of commercial saline cathartics. Her menses had stopped two years ago. Stiffness and aching in both hips and shoulders and in the neck had been present intermittently. There were frequent cramps in the bottom of the left foot. She had frequent colds. She was thin, somewhat pale, and appeared weak and chronically ill. The skin was dry but not thickened. The pulse was 64, blood pressure 115 systolic, 70 diastolic. She was mentally and physically hyperactive and irritable. The red blood cell count was 3,430,000, hemoglobin 67 per cent.

The basal metabolism was minus 28 per cent. Restoration of the metabolic level to normal resulted in complete relief of

the muscular pains and cramps and the constipation. The blood count is improving and she is less nervous and irritable.

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Patients with obesity are nearly always suspected of hypothyroidism, but the basal metabolic rate in my experience is more often normal or elevated. The use of thyroid preparations in obesity without hypothyroidism may be dangerous and is ordinarily unjustifiable. Certain dermatological entities such as atopic dermatitis, ichthyosis, scleroderma, and senile eczema may improve with thyroid medication. In most instances there is no definite evidence of hypothyroidism in such cases but the accelerated skin metabolism may produce the beneficial results. Low metabolism with a marked tolerance for thyroid is seen in nephrosis, as described by Epstein.<sup>3</sup> Diuresis, with lessened edema and general improvement may result in such patients when thyroid is given, but there is probably no true hypothyroidism. Patients with chronic nephritis often closely resemble those with myxedema since both may have pale, puffy faces and bodies, anemia, weakness, and be stuporous or disoriented.

In doubtful borderline hypothyroid cases one should remember that the patient's first metabolism test may give a figure higher than his true basal, and it is wise to repeat such tests. Thyroid conditions are fluctuant, and variable in severity so that metabolism tests repeated at intervals are very helpful. Blood cholesterol determinations over 200 mg. per cent support the impression of a lowered metabolism. Lastly, and of considerable importance: do not discontinue therapy and change the diagnosis if definite results are not apparent in one or two weeks. It may take several weeks or a month to raise the metabolism to normal, and some of the symptoms and signs may not disappear until the metabolism has been normal for some time.

#### HYPERTHYROIDISM

Two classes of patients offer considerable difficulty in the differential diagnosis of hyperthyroidism. One group have an elevated metabolic rate with few or no hyperthyroid symptoms or signs, the other group have striking signs or symptoms with metabolic rates within the normal range. Condi-

tions such as fever, leukemia, pernicious anemia and cardiac decompensation may cause elevated metabolic rates. All the so-called "classic" signs may be present in the absence of true thyrotoxicosis. Exophthalmos may be congenital, the tachycardia may be caused by infection, anemia or heart disease, and the tremors may be a pure nervous manifestation. Nodular or diffuse thyroid enlargement may be present without hypersecretion. The flushed face and tachycardia of mitral stenosis or vascular hypertension are often misleading. The weight loss, tachycardia, gastro-intestinal irritability and nervousness of early pulmonary tuberculosis may cause errors in diagnosis.

Among the nonthyroid conditions with symptoms suggesting thyrotoxicosis, neurocirculatory asthenia is most commonly seen. Hyperthyroid individuals and patients suffering from effort syndrome both complain of palpitation, dyspnea or excess fatigue on exertion, irritability, tremor and emotional imbalance. Both may be hyperkinetic, and suffer from insomnia, phobias and apprehension. The following case report indicates how such patients may be distinguished from those with true hyperthyroidism.

L. M., a married woman of twenty-three, became irritable and apprehensive and complained of rapid heart beat shortly following the birth of her first child. She had had a small diffuse goiter, first noted at about the age of fifteen. At that time she had suffered from similar nervous symptoms, and had been given a medicine she believed to contain iodine, following which the nervous symptoms improved and the goiter became smaller. In the year following the birth of her child she lost 15 pounds in weight. Her face and neck were flushed, there was slight exophthalmos, the thyroid was slightly but diffusely enlarged and there was a slight tremor of the fingers. The pulse ranged from 80 to 115 and the blood pressure was 110 systolic, 65 diastolic. A basal metabolism before hospital entry was reported as plus 16 per cent. Basal metabolism tests after entering the hospital were minus 2, minus 7, and minus 3 per cent. Creatine and creatinine excretion upon

a controlled diet were within normal limits. Blood cholesterol determinations ranged between 125 and 170 mg. per cent. Lugol's solution was administered as a diagnostic test as described by Means.<sup>4</sup> The basal metabolism did not fall, being plus 1 and minus 1 per cent after twelve days, and the creatine and creatinine excretion was unchanged.

True hyperthyroidism may occur in the presence of a metabolic rate falling within the usually accepted normal range of plus 10 to minus 10 per cent. The symptoms and physical signs in such cases are usually borderline in character, but may be quite definite. As contrasted with patients who have neurocirculatory asthenia, the pulse rate at rest remains high, the pulse pressure is increased and there is a fall in the basal metabolism after taking iodine. It must be concluded that the normal basal metabolism in such patients is below or at the lower limit of the commonly accepted normal range. If an individual's normal rate were minus 15 per cent, a figure of plus 10 would represent a 25 per cent elevation. It should be again emphasized that thyroid function is fluctuant and that a truly toxic patient seen during a remission may have a normal rate. Thyrotoxicosis without elevated metabolism has been called the "larval" type or "form fruste." Clute,<sup>5</sup> Troell,<sup>6</sup> Plummer<sup>7</sup> and others have described such patients. Gordon and Graham<sup>8</sup> concluded that it occurs more commonly with nodular goiter (54 of their 71 cases). Cardiac insufficiency, probably the result of a prolonged mild hyperthyroidism, was found frequently in such patients over forty years old with nodular goiter. Subtotal thyroidectomy resulted in clinical cures in 53 per cent of the patients with diffuse goiter, and in 67 per cent of those with nodular goiter. The metabolic rates on the average decreased very little, but pulse rates were slower and pulse pressures diminished.

The following case illustrates the fluctuant nature and diagnostic characteristics of such borderline cases:

**Hyperthyroidism with Normal Metabolic Rate.**—G. S., a man of twenty-seven, had complained of goiter, nervousness, palpitation, and excess perspiration, for several years.

The thyroid had gradually diffusely enlarged. Marked variations were noted from time to time in its size. His skin was flushed and warm; there was definite tremor of the hands. A soft bruit could be heard over the gland. The pulse rate was 100, the blood pressure 150 systolic, 90 diastolic. During two years' observation there were moderate variations in the severity of symptoms and repeated basal metabolic rates averaged plus 6 per cent. At one time iodine was given and the rate fell to minus 1 per cent and the pulse to 84. At another time after three control determinations varying from plus 10 to plus 6, rest and phenobarbital resulted in a fall to minus 6 per cent with a pulse of 80 and blood pressure 125 systolic, 70 diastolic. He is still under observation and thyroidectomy will probably be advised.

#### ADRENAL INSUFFICIENCY

Addison's disease in its fully developed form is fortunately relatively rare. It is not uncommon, however, to encounter patients with less severe symptoms strongly suggesting adrenal hypofunction. Patients such as the one described here represent borderline cases probably more numerous and more responsive to therapeutic efforts than those with more conclusive clinical pictures.

T. C., a man of fifty-six, had suffered from dizzy spells, weakness, constant fatigue, and a gradual increase in skin pigmentation for six months. There was marked pigmentation of the forearms, neck, shoulders and legs. His blood pressure was 120 systolic, 80 diastolic, fasting blood sugar 75 mg. per cent, basal metabolism minus 21 per cent, red blood count 3,900,000 and hemoglobin 80 per cent. The sugar tolerance was as follows: fasting 81, one-half hour after the glucose 109, one hour 106, two hours 88 and four hours 93 mg. per cent. Plasma chlorides were 604 mg. per cent. No excess excretion of sodium could be demonstrated. The patient felt considerably better when given adrenal cortex substance by mouth or by injection. When sodium chloride was withdrawn his symptoms increased in severity. When given



large amounts of sodium chloride by mouth his strength improved and his blood pressure rose somewhat. He was able to walk to the clinic in forty minutes whereas formerly it had taken him one and one-half hours.

It would seem important in such patients at least to prescribe large amounts of salt in the hope of preventing progression of the disease. If further improvement can be obtained with the adrenal cortical hormone, its administration is indicated. Caution, however, must be maintained to avoid the tendency to see adrenal insufficiency in all patients with asthenia. The use of the hormone should be restricted to those cases in which there are definite indications.

#### BORDERLINE DIABETES

Not infrequently patients are seen with only slightly elevated blood sugar and minimal glycosuria. Glucose tolerance tests in such cases usually show mild or borderline types of diabetic curves. At this point we are confronted with a dilemma, emphasized by the recent trend toward higher carbohydrate diets in diabetes. Shall we restrict carbohydrate to spare a failing pancreas, or shall we force carbohydrate to stimulate the islets to increased production of insulin?

Formerly the discovery of a diabetic sugar-tolerance curve led promptly to strict curtailment of carbohydrate intake. We have recently reported observations indicating that some diabetics will gain tolerance on high carbohydrate, while others will lose tolerance.<sup>9</sup> Studies upon the relative response to insulin offer hope that we may be able to distinguish diabetes which is primarily pancreatic from that which is largely extra-pancreatic. The relatively insulin-resistant diabetic who reacts as if his disease were at least partially extra-pancreatic in origin usually shows definite gains in tolerance with liberal carbohydrate. Those patients in the relatively insulin-sensitive group usually lose tolerance with excessive carbohydrate ingestion. An effort to determine the relative insulin sensitivity of the patient would therefore seem in-

licated before selecting the individual diet in borderline cases of diabetes.<sup>10</sup>

When a sugar-tolerance curve of the mild diabetic type is found it is well to take into consideration the possible effect of the patient's diet immediately preceding the test. It has been demonstrated that a starvation or high-fat diet decreases the glucose tolerance in normal subjects, while a high-carbohydrate diet raises the tolerance.<sup>11</sup> When careful study of tolerance curves is indicated we have found it useful to employ a preceding standard diet of 27 calories per kilogram body weight, containing 2 Gm. of carbohydrate per kilogram.

#### SPONTANEOUS HYPOGLYCEMIA

Hypoglycemia severe enough and protracted enough may provoke a chain of symptoms characterized by tachycardia, hunger, weakness, sweating, tremor, diplopia, mental confusion, sometimes delirium or convulsions, and finally coma. Hypoglycemic symptoms may occur in many conditions:

1. Excess of insulin.
  - (a) Therapeutic injections.
  - (b) Pancreatic islet tumor or hyperplasia.
  - (c) Functional hyperinsulinism.
2. Diminution in insulin-resistant factors.
  - (a) Adrenal disease (Addison's disease).
  - (b) Pituitary disease (Simmond's disease, pituitary tumors).
  - (c) Thyroid disease (myxedema).
3. Diminution of glycogen reserves.
  - (a) Starvation.
  - (b) Liver disease.
  - (c) Renal diabetes.
  - (d) Lactation.
  - (e) Muscle wasting or excessive muscular exercise.
4. Disturbance in central nervous system control of blood sugar.

**Differential Diagnosis.**—Patients suffering from spontaneous hypoglycemic attacks have been suspected of drunk-

eness, of having brain tumors, epilepsy, hysteria and various psychoses. The association of hunger and of relief by food is suggestive of hypoglycemia. The onset of the attacks with exertion and with fasting is characteristic. Sugar-tolerance tests are not reliable diagnostic aids since even diabetic type curves may be obtained as well as the more characteristic flat or depressed curve. Detection of a blood sugar below 40 mg. per cent during an attack and quick relief by intravenous glucose are conclusive evidence of hypoglycemia as the cause of the symptoms.

Following the establishment of the diagnosis of spontaneous hypoglycemia the determination of possible causes must be undertaken. There is at present a tendency to use too loosely the term "hyperinsulinism." It should be employed only in those cases in which no other cause can be demonstrated for the low blood sugar. Even after a probable diagnosis of hyperinsulinism is made an important decision remains. Is it functional or may an islet adenoma be present? Operative removal of such adenomata has resulted in cures in several cases.

Acute fulminating cases, in which loss of consciousness is frequent and intravenous dextrose is required, and in which there is no favorable response to diet should have exploratory operations. Certain puzzling borderline cases present real problems, as illustrated in this report:

W. B., a girl of twenty, had suffered from spells of extreme nervousness, and occasional attacks of loss of consciousness for four years. A typical attack began with nervousness, tremor, hunger, weakness and faintness. She would then burst into a profuse perspiration and slip into unconsciousness without preceding convulsions. Awakening after an hour or two she would be very weak, hungry and thirsty and would revive rapidly after taking food. She was slightly obese and had been gaining weight. Basal metabolism was minus 2 per cent. A glucose tolerance test showed practically no rise in the blood sugar: fasting, 66 mg. per cent; one-half hour, 69; one hour, 63; two hours, 67; three hours, 62. A fasting sugar of 55

mg. per cent was obtained at another time. During an attack the blood sugar was 72 mg. per cent but intravenous glucose promptly terminated a typical seizure usually lasting over an hour. A high-fat, low-carbohydrate diet was given with frequent feedings and no further attacks have occurred.

A diagnosis of functional hyperinsulinism was made in this case because of the prompt response to a diet designed to decrease the amount of insulin secreted.

#### ADRENAL CORTICAL TUMORS AND PITUITARY BASOPHILISM

Obesity, hypertension and decreased sugar tolerance are among the most common conditions encountered in medical practice. Frequently they occur in the same patient. The occurrence of various grades of hirsutism in women is not uncommon. Menstrual disturbances, especially amenorrhea, occur often in obese women. If the more common triad of obesity, hypertension and diabetes occurs in association with the rarer conditions of hirsutism and amenorrhea we have the symptom complex occurring in the adrenocortical syndrome and the indistinguishable "pituitary basophilism." Since in certain cases removal of adrenal tumors<sup>12</sup> or roentgen therapy to the pituitary<sup>13</sup> has resulted in relief, every effort should be made to diagnose these more serious conditions from the more frequent borderline cases which resemble them. The problem is further complicated by the possibility of another uncommon tumor which may cause amenorrhea and hirsutism, the ovarian arrhenoblastoma.<sup>14</sup>

Our differential diagnostic methods are at best gross and inadequate in these conditions. In all such cases both positive and negative evidence should be considered.

The ovary is the most accessible to examination. Gynecologic examination may reveal a tumor of the ovary which can be removed. Complete amenorrhea with deep male voice, assumption of male contours, enlarged clitoris, and atrophy of the breasts are much more suggestive of arrhenoblastoma than of pituitary or adrenal disease.

The pituitary and adrenal are more difficult to examine.

Local pressure changes in the presence of a pituitary neoplasm may cause headaches, visual failure, constriction of the visual fields, or roentgenographic alterations in the sella turcica. However, most of the basophilic adenomata described have been very small and such neighborhood signs have not occurred. Frank diabetes or a prediabetic state may occur either with adrenal cortical tumors or pituitary disease. The basal metabolic rate may be at any level, from that of myxedema to that of hyperthyroidism, but is usually normal. A palpable mass may be present in the loin in the larger adrenal neoplasms, but only a small adenoma or simple hyperplasia may be present. Obesity of the "buffalo" or "Humpty-Dumpty" type, confined to face, neck, and trunk, purplish abdominal striae, osteoporosis, polycythemia, exophthalmos, and purpura have been described as particularly suggestive of pituitary basophilism.

It is questionable whether symptomatically the pituitary can be distinguished from the adrenal syndrome. Whenever definite signs point to one or the other organ, therapy may be correspondingly directed. From the present evidence it seems that either gland may initiate the changes described.

#### SUMMARY

The chief value of the rapidly accumulating knowledge of the endocrine glands should be in the better understanding of minor or moderate functional deviations from the normal. The good response to therapy and the frequency of the less severe glandular disturbances makes it important to keep them in mind.

That endocrine disorders may not present classical syndromes deserves emphasis. A few cases are presented illustrating signs and symptoms probably occurring frequently but usually neglected in endocrine diagnosis.

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## CLINIC OF DR. MAX DEUTCH

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### THE DIAGNOSIS AND TREATMENT OF ENDOCRINE INFANTILISM

DWARFISM is the normal occurrence in the various tribes of pygmies that are scattered through Africa and various Asiatic islands. Pygmies usually attain a height of 4 to 4½ feet in adult life, mature sexually at the age of ten or eleven years, are short-lived, dying as a rule at the age of about forty, and retain throughout their lives the infantile proportions of short limbs and relatively long torso. Their features in the face, hands, and feet are distinctly simian in type and they are considered by anthropologists as of very remote origin.<sup>1</sup>

A normal type of dwarfism is seen occasionally as a familial feature, possibly as an atavistic phenomenon. We have had the opportunity of observing some of the members of such a family in which the somatic hypoplasia is seen to be transmitted through normal as well as dwarfed members of the family, as seen in the accompanying genealogic tree (Fig. 15). The dwarfed members of this family were very small at birth, as far as could be determined, weighing only 4½ to 5½ pounds, although full term. None of them show any evidence of glandular disease. As regards function and span of life they lead normal lives. The adult members have extremities somewhat short relative to the length of the trunk. In the one adult who has been studied roentgenologically, the bone development is normal. In all four of the children who have been x-rayed, there is distinct evidence of delay in the



appearance of the centers of ossification as compared with children of average normal size.

Very striking instances of sporadic dwarfism occurring in families of average stature have been reported. One of the first records was by von Hanseemann<sup>2</sup> in 1902, who studied a professional midget. This man, at twenty-two years, was 3 feet 10 inches in height, had normal adult proportions, normal bone development, normal hair growth on face and pubes; and although the testes were not palpable, he gave a history of nocturnal emissions, suggesting at least normal interstitial

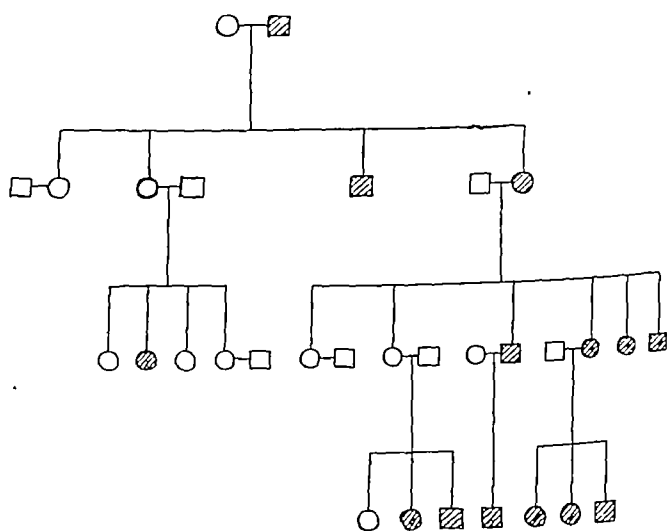


Fig. 15.—Familial somatic hypoplasia. The shaded symbols indicate subnormal size, the adult members being 5 feet or less.

cell function. Von Hanseemann called this type "Primordial Dwarfism," and thought it was probably due to an ovum defect.

Dwarfism is also associated with congenital bony or cartilaginous anomalies. Of these the most common is chondrodystrophia fetalis, in which the shortness in stature is considered due primarily to defective cartilage formation, particularly at the ends of the long bones. The bones themselves are widened and deficient in calcium. Other congenital bone defects, such as cleidocranial dysostosis and osteogenesis im-

perfecta, may be accompanied by dwarfing. Of the acquired bone diseases, rickets, whether due to vitamin D deficiency, renal disease, or celiac disease, may be responsible for marked stunting of growth. Dwarfing also may occur in diabetes, congenital syphilis, and congenital heart disease; in fact, as a result of any severe chronic or recurrent disease in childhood.

To be distinguished from mere dwarfing in stature is the condition of infantilism. This term should be restricted to those who are not only considerably below standard size but who also exhibit retarded sexual development. Often such individuals also retain the infantile body proportions with relatively short extremities as compared to the trunk. (Normally the pubic height becomes equal to the upper measurement, from vertex to pubis, at twelve to fourteen years.)

True infantilism has been reported to accompany hemolytic icterus at times. Langston<sup>3</sup> recently reported a boy, whose growth became retarded at the age of seven years, and whose development ceased entirely at the age of eleven. At the age of eighteen years, he was not quite 5 feet in height. In addition to anemia, icterus, splenomegaly, and increased red cell fragility, he had marked sexual underdevelopment as regards genitalia and hair growth. His bony development was markedly retarded. Following splenectomy he was given antuitrin G and the pregnancy urine extract, but in amounts hardly sufficient to account for a growth of 6½ inches in height and the occurrence of sexual maturity in the two years following the splenectomy.

In the presence of von Gierke's disease, which is a syndrome of hepatomegaly and deficient glycogenolysis, infantilism in 3 siblings was recently reported,<sup>4</sup> the most marked case being in the oldest, a boy of eighteen years who, although normal at birth, began to slow up in his growth at the age of three and one-half years, at which time a large liver was first noted. At the age of eighteen he had the appearance, size, proportions, and sexual development of an eight-year-old.

Cretinism has long been recognized as a type of infantilism

of endocrine origin. The striking efficacy of thyroid extract in most cases is well known. The accompanying chart (Fig. 16) illustrates this remarkable effect on growth in a typical cretin who was first seen in the pediatric clinic at the age of five and one-half years, but whose mother did not carry out the directed treatment until the child's return to the clinic five years later.

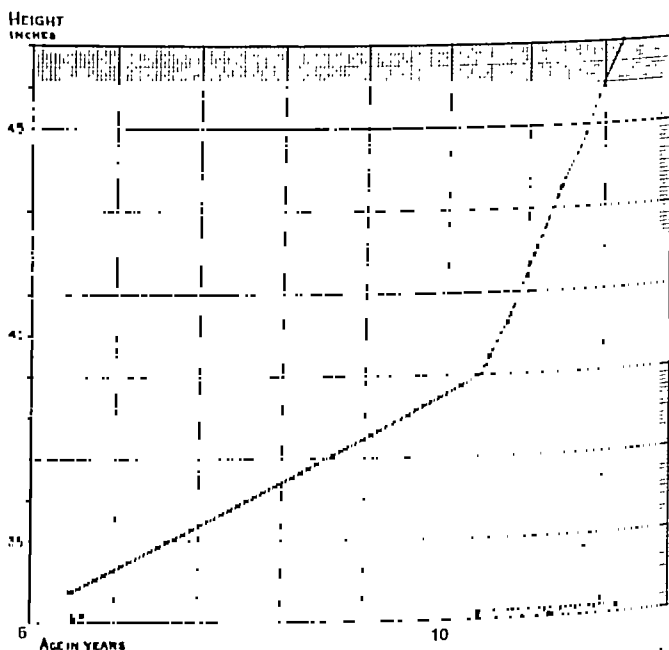


Fig. 16.—Effect of thyroid therapy on growth rate of a cretin. Shaded strips indicate periods of thyroid administration.

The occurrence of stunted growth in a child with hypothyroidism even in the absence of cretinism is illustrated by the following case.

This child (Fig. 17), Marilyn P., was first seen in the pediatric clinic October 18, 1932, at the age of eleven and one-half months, because of anorexia and short stature. The mother, twenty-two years, is of average stature; the father, a man of twenty-four, is somewhat below average size. A paternal aunt has a colloid goiter and is overweight. A maternal second cousin has hyperthyroidism. The child was

born about one week beyond the calculated term after a normal pregnancy, weighing  $5\frac{1}{4}$  pounds at birth. She was a normal baby except for the small size, and did well on breast feedings until the age of five weeks, when she began to vomit projectily. The vomiting ceased shortly after a pyloroplasty at the age of six weeks, but she has remained a feeding prob-



Fig. 17.—Marilyn P. Hypothyroid dwarfism without cretinism.

lem ever since. She has been markedly constipated, the bowels moving as a rule only once in three days. Her skin has always been dry. Her development is retarded. She cut a tooth at ten and one-half months, and at the age of eleven and one-half months did not sit up alone. Because of the dry skin and constipation she had been given thyroid ex-

tract in doses of  $\frac{1}{4}$  to 1 grain three times a day for irregular periods totalling about three months. Thyroid had been administered for only short periods at a time because it resulted regularly in excessive sweating, restlessness and sleeplessness.

Between October, 1932, and January, 1935, she was seen at irregular intervals in the pediatric clinic and in Children's Hospital. During this time she was given thyroid extract (Armour) in doses of from 1 to 3 grains daily at various times for a total of seven months. Rather quickly, however, she developed signs of nervousness, sweating, sleeplessness, and hair loss, with little or no improvement in appetite; and although growth improved, there was very little gain in weight.

Since January 15, 1935, the child has been under close observation in the endocrine clinic, and the mother has been very cooperative so that careful observation for over a year has been possible. At the start of this period, the patient, aged three years two and one-half months, weighed 22 pounds 7 ounces and measured 32 inches (average height for eighteen months). Her nutrition was fair, the weight being only  $1\frac{1}{2}$  pounds below the average for her height. The facial expression was dull, the features full, but without the retrousse nose or large tongue characteristic of cretins. Epicanthic folds and a slight incurvation of the little finger were present, but other signs of mongoloidism were absent. The skin of the face, neck, back, and especially the hands was dry. The hair also was somewhat dry, especially over the occiput. The fingers were not the stubby digits of cretinism. All the deciduous teeth were present. The heart and lungs were normal. The abdomen exhibited a right rectus scar at the site of the pyloroplasty; abdominal prominence was not excessive. No organs or masses were palpable in the abdomen. The external genitalia were normal. Mentally she was obviously retarded.

Hemoglobin, 65 per cent; red blood corpuscles, 3,450,000. Serum cholesterol, 572 mg. per 100 cc. x-Rays of the wrists taken on August 29, 1934, at the age of two and  $10/12$  years showed only 1 carpal center, no centers for the heads of phalanges, metacarpals, or lower end of radius, although on

February 14, 1935 (aged three years three and one-half months) most of the latter centers, as well as a rudimentary second carpal center, had appeared (Fig. 18).

February 5, 1935, after she had been without thyroid for four months, the administration of  $\frac{1}{8}$  grain daily of thyroid extract (Armour) was begun. She was kept on this for one

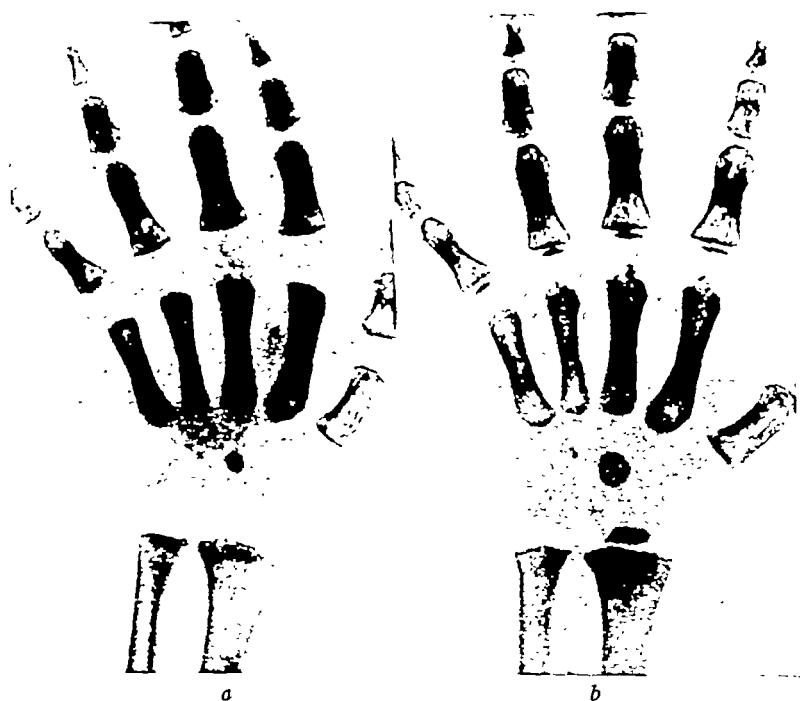


Fig. 18.—Marilyn P. x-Rays of hand and wrist at two and ten-twelfths years (a) and three and three-twelfths years (b), showing delay in bone development. At three years there normally are present three well-developed centers in the carpus and all the centers at the ends of the phalanges and metacarpals.

month and then reduced to  $\frac{1}{10}$  grain daily because of restlessness and excessive perspiration. Her appetite improved, her bowels were less constipated, the cholesterol dropped to 202 mg. on March 4, 1935. Her height in the course of three months increased  $\frac{1}{4}$  inch. The skin and hair became distinctly less dry.

After two weeks without specific medication, the administration of the thyrotropic growth factor of the anterior pituitary (Phyone)\* was begun, starting with 0.25 cc. subcutaneously, and increasing to 1.5 cc. In the course of five weeks she was given 26 injections totalling 26.5 cc. During this period improvement continued as regards skin and hair texture and bowel regularity. There was also about  $\frac{1}{2}$  pound gain in weight. The cholesterol rose, however, to 400 mg. and

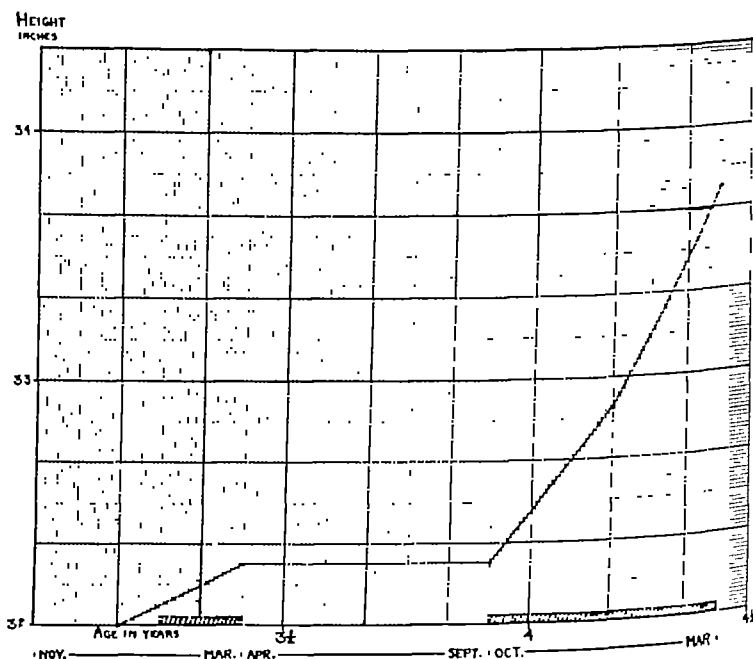


Fig. 19.—Marilyn P. Effect of thyroid therapy on growth rate. Shaded strips indicate periods of thyroid administration.

there was no increase in height. The child then remained away from the clinic for four and one-half months, getting no specific treatment during this period. She gained 12 ounces during this time, but did not grow taller. She was having a normal bowel movement every two days. The hair over the occiput was rather dry, the skin of the upper extremities was fairly dry and of the back very dry. During the next six

\* Supplied to us by Wilson and Co.

months she was constantly on thyroid. This was started as  $\frac{1}{8}$  grain daily (Armour) and slowly increased to  $\frac{3}{8}$  grain daily. Since the latter dosage was accompanied by symptoms of sweating, irritability, and sleeplessness, the amount was reduced to  $\frac{1}{4}$  grain daily. During this six months' period the patient has shown very considerable improvement. She has grown  $1\frac{1}{2}$  inches, which is slightly above the normal rate of growth for this age (four years) (Fig. 19). She has gained almost 2 pounds and has begun to walk and talk. Her bowel movements occur every one or two days. There is still slight dryness of the hair over the occiput and the skin of the back. x-Ray of the wrists still shows considerable retardation; and the child's height at the age of four years five months is the average for a two-year-old. She has been walking since the age of four.

Briefly, then, this child, who was rather small at birth, has remained considerably undersized, and although not presenting the appearance of cretinism has many other typical signs of hypothyroidism: mental deficiency, dry hair and skin, constipation, anemia, delayed bone development, and high cholesterol. She has shown her greatest period of improvement during a six months' period on very small doses of thyroid, carefully regulated so as to minimize overdosage effects. Extreme sensitivity to overdosage of thyroid in cretins<sup>5</sup> as opposed to the high tolerance of normal children<sup>6</sup> is well known.

It is my feeling that this patient can be considered as an instance of hypothyroid dwarfism despite the absence of cretinism. Other cases of this type of "nanosomia hypothyrotica" in later life have been described by Sternberg.<sup>7</sup> Wells<sup>8</sup> described the postmortem examination of a seventy-two-year-old, mentally retarded dwarf, who showed none of the features of cretinism although the only thyroid tissue found postmortem was an atrophic cystic lingual goiter. Hypothyroid infantilism without cretinism appears to be rare.

Of greater interest is infantilism of hypophyseal origin, reports of which have become increasingly frequent in the



literature since the isolation of growth factors from the anterior lobe of the hypophysis.<sup>9, 10</sup> This type of infantilism is known variously as Paltauf dwarfism<sup>11</sup> or the Lorain-Levi type of infantilism,<sup>12</sup> although it was really Gilford<sup>13</sup> who, in introducing the term "ateleiosis," first suggested that the condition was probably of pituitary origin.

Patients with pituitary infantilism may be normal at birth. They develop and grow normally until sometime in childhood, when growth and sex development cease or become greatly retarded. The age of onset is usually between eight and twelve years, but sometimes as early as one year, sometimes as late as fifteen years. Some cases may resume their growth after a period of years, in what would ordinarily be considered adult age. As part of the sexual underdevelopment, there is characteristically a marked delay in epiphyseal closure, although the time of appearance of the centers of ossification is normal. There have been few cases of this condition which have been studied postmortem, the majority revealing tumor destruction or compression of the pituitary, others with Rathke's pouch or craniopharyngeal duct tumors in which the pituitary has shown little or no histological change.<sup>14</sup> Three somewhat atypical cases have been reported in which there were midbrain tumors with no histological change in the pituitary.<sup>15</sup> The cases reported clinically are greater in number than the pathologically studied cases, and of these very few have shown evidence of tumor or other destructive intracranial lesions. The following case is clinically typical of hypophyseal infantilism.

This girl, Lillian S. (Fig. 20), was referred to the endocrine clinic December 6, 1934, at the age of sixteen years because of failure to grow. Her mother and father were both of average size. The patient was born at full term and was apparently normal. Her development and growth in infancy were normal. When she was seen in the pediatric clinic at the age of eight years because of chronic otitis media, no deficiency in stature was noted. At the age of twelve years, the child's growth almost ceased, although there apparently had

been a growth of 1 inch in the nine months preceding her entrance into the endocrine clinic. She had never menstruated. Frontal headaches, usually in the evening, had been



Fig. 20 —Lillian S., aged sixteen years. Hypophyseal infantilism with dwarfism and sexual underdevelopment.

present for about two years. Examination: height, 52 inches; pubic height,  $26\frac{1}{2}$  inches; weight, 73 pounds. She was well nourished and presented the appearance and approximate body proportions of a ten-year-old. There was slight fatty fulness

over the breasts, abdomen, and buttocks. The external genitalia appeared normal for a girl of nine or ten years. There were a few sparse hairs over the labia majora. The uterus (rectal examination) was infantile. The skin was warm, moist, smooth. The hair of the head was normal. A few sparse axillary hairs were present. The facial expression was rather mature, the features small, with pointed nose and chin, high narrow palatine arch, and crowded teeth. There was a chronic otitis media and chronic tonsillitis. Heart and lungs were normal. The blood pressure was 110/80. The eyes and eyegrounds were normal except for hyperopia, with vision of 6/60 in each eye. The visual fields have not as yet been determined. The I. Q. was 84.

Basal metabolism, + 17. Wassermann and Kahn, negative. Urine contained sugar on one occasion. Stereogram of skull showed a small, bridged sella turcica. The bones of the skull, face, and cervical spine were of delicate structure. A lateral view of the elbow revealed partial union of the head of the radius, nonunion of the olecranon. The hand and wrist showed normal bone development. However, there was no union of any of the centers at the ends of the phalanges and metacarpals or lower ends of radius and ulna.

During a period of six months' observation without specific medication, the patient grew only 1 cm. (0.4 inch). The subcutaneous administration of anterior pituitary hormone (Phyone) was then begun.\* She was given 1 to 2 cc. two to three times weekly for a period of three months, a total of 48 cc. being administered. About this time the patient developed a pathological depression because of home factors and treatment could not be continued. A check of her measurements on April 7, 1935, ten months after the start of endocrine therapy, revealed a growth of only 1 cm. (0.4 inch) in this period.† x-Ray of the hand and wrist at this time (age seventeen and one-half years) showed no change from the ap-

\* Under the supervision of Dr. Cyril M. MacBryde.

† The measurements of both patients were made by Dr. Cecil M. Charles of the Department of Anatomy.

pearance one and one-half years before (Fig. 21). Her general appearance was unaffected except for a slight increase in the amount of pubic hair.

This patient, it is seen, showed no beneficial effect of the pituitary therapy, which was probably grossly insufficient. Since many of the injections were accompanied by moderately



Fig. 21.—Lillian S., aged sixteen years. x-Ray of hand and wrist, showing nonunion of epiphyses. The same appearance is found in a film taken one and one-half years later. Union of all the centers at the ends of phalanges and metacarpals is normally complete at fifteen to sixteen years.

severe local reactions, administration of larger amounts than 2 cc. was not attempted.

Reports on the effectiveness of growth hormone have shown a great variation in individual cases. Using pituitary extracts relatively high in growth-promoting principle, Shelton and his coworkers have noted varying degrees of refractoriness in their patients. As a rule, the older the patient the more

refractory he was, irrespective of the status of his epiphyses.<sup>16</sup> Furthermore, all children show variations in the growth curve from year to year, and particularly from month to month, the growth increment being greater in the semester of April to September. In considering the effectiveness of any therapy in stimulating growth, not only must this be borne in mind, but also at least six months' control period before and after therapeutic courses should be carried out in order to judge the effectiveness of the therapy. The best results in stimulating growth have been reported in individuals who received thyroid as well as growth hormone.<sup>17</sup>

In the administration of thyroid gland, particularly to children, two principles must be borne in mind. (1) Children with hypothyroidism are sensitive to overdosage effects. The initial dose should therefore be low, preferably not more than  $\frac{1}{4}$  grain daily of the desiccated gland. (2) There is no satisfactory criterion for the amount of thyroid that should be given except the clinical reaction of the patient. Since the overdosage effects that may result are temporary and subside within a few days after discontinuing treatment, it seems reasonable to increase the daily dosage of thyroid at intervals of two to four weeks until manifestations of overdosage do appear.

Therapy with the growth factor is still in an unsatisfactory state. On the basis of body weight, results in human beings to be comparable with those in experimental animals would require the administration of enormous amounts of the extract. If possible, injections of 2 cc. daily or every other day should be given deep subcutaneously, although smaller doses ( $\frac{1}{4}$  to  $\frac{1}{2}$  cc.) should be used at the start because of the local reactions in some individuals. Hartmann<sup>18</sup> has suggested that the growth hormone be given on alternate months so as to minimize the formation, if such does occur, of "anti-hormone." As a matter of fact, of several undersized diabetic children whom he has treated, the only one in whom a possible growth stimulation occurred was a boy that was treated in this fashion.

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## CLINIC OF DR. HAROLD A. BULGER

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### ENDOCRINE OBESITY

CLINICAL experiences repeatedly suggest a relationship of obesity to the endocrine glands. To postulate such a relationship seems rational. It is clear that various endocrine organs may have a more or less striking influence on metabolic processes. They may cause variations in the total energy expenditure or defects in intermediary metabolism. Certain hormones have characteristic effects on specific cells and therefore might be expected to act locally on adipose tissue.

Early expectations that diminished combustion from thyroid insufficiency would explain all obesity have proved a delusion. Hypothyroidism is rarely, if ever, a primary cause of marked obesity. A lowered specific dynamic action of foods had been postulated as an explanation for a conservation of calories. Certain of the endocrine glands have been thought to exert such an influence. The most careful investigations, however, have not presented evidence that this in itself was an adequate explanation. An exaggerated drop in metabolic rate after exercise or food to below figures considered the basal rate has been noted in obesity, and purported to be significant. However, such "negative phases" are elusive in obesity and striking examples may be found in undernutrition.

Body weight is maintained at a remarkably constant level in the great majority of normal individuals. This significant fact tends to be true even with markedly different habits of



activity and food consumption. It seems obvious that food intake cannot be so delicately regulated that day by day it would just balance the actual requirements for activity. Appetite could not possibly discern the slight variations in caloric intake which would be necessary. The "factor of safety" possessed by various structures and functions of the body is well known. One might suggest that a "factor of safety" is operative in regard to the food intake. Food intake may always tend to be greater than is actually necessary for activity, and other metabolic needs. One might postulate that, normally, there are mechanisms which may limit the storage of food and dissipate excess calories. Abnormalities of these mechanisms would result in states of undernutrition or obesity. It is conceivable that the abnormality may be located in the stores, in the adipose tissue itself.

The usual response of starvation or inadequate food intake is a lowering of the basal metabolic rate. This at once suggests a means by which body weight may be automatically regulated. An increase in metabolic rate with excessive food intake had been noted in animals. This has been discussed at great length and is usually referred to as "luxus consumption." It has been inferred that this effect may be influenced by the endocrine glands. The subject has received little attention from this point of view. Studies have suggested that "luxus consumption" no longer occurs after thyroidectomy. The effect is said to be normal after removing the gonads. It seems, however, that a phenomenon as simple as "luxus consumption" is not prominent in the human body. While undernutrition decisively lowers the basal metabolic rate, an excessive food intake, in experimental studies, has not produced a significant rise.

Two cases are presented, chiefly to illustrate the difficulty of detecting a metabolic explanation of obesity. The two girls are of comparable ages. Their histories are similar except that one developed marked obesity, the other emaciation. They were both referred to the endocrine clinic, as they were thought to have endocrine abnormalities.

**Case I** was a sixteen-year-old girl. At thirteen years, menstruations started. They were regular and normal. Then, after about a year, they became scanty and finally amenorrhea developed. Her weight had always seemed normal. At thirteen she weighed 120 pounds. Some time after that she began to gain weight rapidly. When first seen she weighed 204 pounds. She had obscure painful areas over various parts of the body. All evidence indicated that she was not a big eater; appetite was considered to be rather poor. Her school history indicated definite personality changes during this time. The school nurse found her temperature slightly elevated over long periods. Before the onset of these disturbances, she had had an illness lasting several months which may have been encephalitis. A sister had had a "nervous breakdown."

Although she appeared sturdy and strong, there was actually considerable asthenia. There was nothing notable about the distribution of the adipose tissue. The development of the secondary sex characteristics seemed normal. Pubic hair extended up over the lower abdomen. There were rose-colored striae over the abdomen and upper arms. Blood pressure was usually a little elevated; average about 136/90. There were changes in skin circulation, varying from a definite diffuse pink flush to mottled areas of cyanosis. There was no tendency to ecchymosis. The sugar tolerance curve was as follows: fasting, 82 mg. per cent; one-half hour, 261; one hour, 192; two hours, 73, and three hours, 82. The basal metabolic rate was moderately elevated (+17 to +25 per cent).

**Case II** was a girl sixteen years old. At fourteen years, menstruations started. After a little more than a year amenorrhea developed. She had been a rather small girl, at eleven years weighing only 87 pounds. With the onset of menstruations she started to gain weight rapidly until she reached 129 pounds. Then, before the amenorrhea started, she began to lose weight; weight fell to 89 pounds. There had been no striking change in food intake; appetite was good. Her

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hips, buttocks and upper thighs. Overdevelopment in these locations, when the obesity is not marked, may occasionally appear significant. Usually, however, they are obscured by the more general fat accumulation.

More difficult to discuss are the variations in firmness and resilience of adipose tissue. These, combined with differences in strength and tension of the supporting tissues, may result

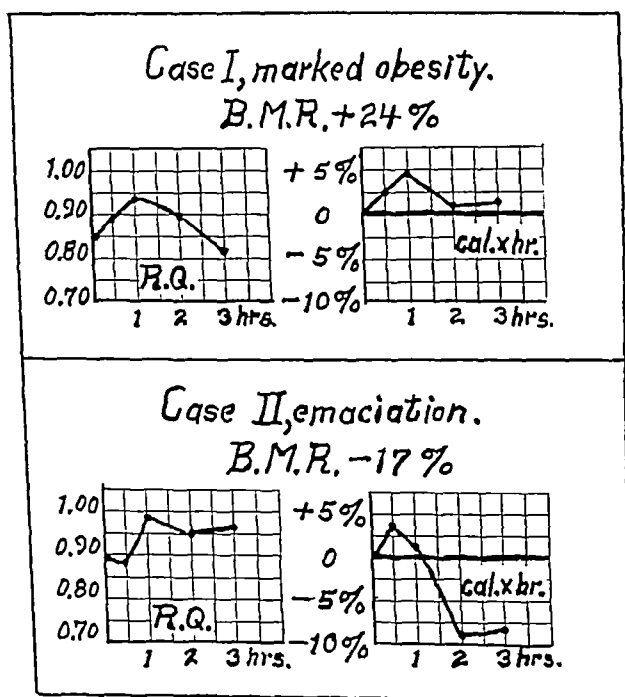


Fig. 22.—Comparing metabolic studies on Cases I and II. They show the respiratory quotients and the percentage change in calories per hour after glucose.

in apparent changes in distribution. One frequently sees diagnostic significance attached to these aspects, but in reality they seem to be related more to age, general physical condition, or duration of obesity. There is another obscure effect in which gravity appears to play a part. We refer to the increase in adipose tissue in dependent parts. This seems to occur at times even when the upper parts of the body are

family insisted there had been a noticeable gain in height between the ages of fourteen and sixteen years.

There was nothing of note in her early history except a tendency to constipation. One sister had been operated on for a goiter. Another sister had developed amenorrhea at about the same age as the patient and had become moderately obese at the time. Later she reverted back to normal health.

This patient presented nothing of special note on examination except the obvious thinness. Blood pressure tended to be low, average about 98/54. The sugar tolerance curve was low: fasting, 76 mg. per cent; one hour, 90; two hours, 105; three hours, 87. The basal metabolic rate was moderately low ( $-17$  to  $-22$  per cent).

Some metabolic studies on these two patients are shown in Fig. 22. The basal metabolic rate of the patient with obesity was elevated; that of the patient who had been losing weight was low. The fasting respiratory quotients and the respiratory quotients after glucose were about the same in the two patients. The undernourished patient rather than the obese patient presented a good illustration of a "negative phase" of the metabolic rate following the specific dynamic action of glucose.

Many writers, seemingly with the greatest confidence, attach vast significance to variations in the distribution of fat. One pleads for a more critical attitude. Constitutional make-up is probably the greatest of the factors influencing the pattern of fat distribution. As inheritance determines such features as stature and character of the hair, it must determine the form of the deposits of adipose tissue. About two thirds of the individuals with obesity have a family history of corpulence. Local fat accumulation seems related to the activity of the gonads. One notes the development of adipose tissue in certain areas giving the body the contours which are such important features of the secondary sex characteristics. This development is more striking and typical in the female. The particular areas responding to this influence are the regions of the breasts, shoulder girdles, umbilicus, mons veneris.

The symptomatology, in addition to the obesity, presents a tendency toward genital dystrophy, and in children abnormalities in growth. There are often variations in carbohydrate metabolism. Features vary according to the age of onset. In infancy and childhood before puberty, it is characterized chiefly by the obesity. Any evidence of genital dystrophy, of course, would hardly be expected. In this period we find the tendencies toward abnormal growth. Rarely is the stature less than normal. Frequently there is a period of increased rate of growth. Sometimes this may be quite striking. When fully developed, however, these patients are seldom abnormally tall and are often below the average height because epiphyseal closure occurs prematurely and results in an early cessation of growth. Sluggishness and somnolence are common. In the early stages, the sugar tolerance curve may be higher than normal.

Later on, around the age of puberty, changes relative to the secondary sex characteristics become evident. There is a more or less marked tendency for the sex organs to be underdeveloped, although it is not unusual for the development to occur several years earlier than normal. In males the axillary and pubic hair is scant or absent. Adipose tissue at first may increase in the regions of the breasts, mons veneris and hips, giving to the male the configurations of a female. As the obesity becomes more marked, however, these contours may become obscured. In the female there is a tendency toward amenorrhea. One often obtains a history of normal or excessive menstruation and periods of amenorrhea. Related, perhaps, to the transient periods of increased stimulation of development, one may find great variation in the size of the breasts. In some female cases there is little or no enlargement, while in others there is excessive development along with an exaggeration of other female contours by hypertrophied adipose tissue. Whereas, as noted above, there may be, early in the course, an elevated sugar tolerance curve, a flat curve is characteristic of this period. Here again there seems to be a suggestion of deviation from normal in both

becoming thinner. This tendency was recognized by Benjamin Franklin when he wrote in his famed letter to a young man, "The face first grows lank and wrinkled—then the neck, then the breasts and arms—the lower parts continuing to the last as plump as ever: so that covering all above with a basket and regarding only what is below the girdle, it is impossible of two women to know an old from a young one." The condition known as lipodystrophy may be an exaggeration of this phenomenon. Such transitions in obesity are probably not uncommon. Should we not, therefore, be more critical regarding the diagnostic significance of adiposity of the extremities? One should also keep in mind the fact that edema, myxedema tissue, atrophy of the muscles, etc., may modify the form of the obese individual.

One large group of adiposities may be considered as a whole. They seem, possibly, related directly or indirectly to the endocrine system. The clinical pictures suggest that they may be variants of the same fundamental disorder. Various designations have been applied to members of this group: cerebral adiposity, adiposogenital, dystrophia adiposogenitalis, syndrome hypophysaire adiposogenital, Fröhlich's syndrome, adiposis dolorosa, Dercum's syndrome, etc. Etiologically, there is evidence for the involvement of related mechanisms. Hypophyseal tumors are found in this group. There are other types of intracranial tumors. The most common are craniopharyngiomas, congenital tumors of Rathke's pouch, exerting pressure on the pituitary and the hypothalamus. There are rare cases with pineal tumors. Cases have clearly followed encephalitis where the centers in the base of the brain are characteristically involved. They have followed chorea. Many cases occur during growth. It is not entirely irrational to postulate instability of the hypothalamus mechanisms during this period. One can also postulate effects on an hypothalamohypophyseal mechanism secondary to other marked endocrine disturbances; for example, in the extreme adiposities which have rarely followed complete oophorectomy in women.

obesity. Slight to moderate obesity is a characteristic part of the picture associated with increased cortico-adrenal activity, while undernutrition is the tendency in adrenal insufficiency. The rare association of obesity and pineal tumors has been noted above. Animal experiments have indicated that removing the gonads will not cause obesity. However, the changes in adipose tissue at puberty, the tendency toward obesity at the menopause, and the occasional marked obesity of castrates suggest some relation to the sex glands. This relation is possibly due to secondary changes initiated in other endocrine glands or the nervous system. It is conceivable that all marked adiposities are intimately related to abnormalities of the neurohypophyseal mechanisms.

Concerning treatment, the chief point to emphasize, at the present time, is that there should be a more conservative use of drugs and more radical use of diets. It would seem that thyroid should not be used except when there is sluggish mental activity and a distinctly low basal metabolic rate. One notes that it is a common practice to give thyroid to a rapidly growing, slightly obese adolescent, with a moderately lowered metabolic rate, although appearing healthy, active and alert mentally. One doubts that this is advisable. There is no knowledge as to what extent such tinkering may upset neuro-endocrine equilibria. There is nothing to note regarding any efficacy of other endocrine preparations. It seems obvious that dinitrophenol should not be used in the treatment of obesity.

The most important consideration in the treatment of obesity is dietotherapy. Patients must be made to utilize their stores of fat. With marked obesity this will mean a most radical dietary regimen. One should aim to give adequate protein, vitamins and salts with almost no fat and minimal amounts of carbohydrate. One Gm. of protein per kilogram of estimated normal weight will be adequate. The diet should include a pint of skimmed milk daily and citrus fruits. It may be advisable to include haliver oil and yeast. Low carbohydrate vegetables, of course, are given. In the extreme



directions. We have been impressed by the number of cases of severe diabetes in girls with overdevelopment of the female characteristics, moderate obesity, and amenorrhea. They probably belong to this group. One should note the tendency toward abnormal levels of body temperature, delicate skin, small terminal phalanges, small thin fingernails, and genu valgum.

In adults the features other than marked obesity are less striking. Female sexual changes are indicated by the tendency toward amenorrhea. In males the fat deposits may have the same feminine distribution and the sex organs may suggest some reversion toward the infantile type. In this group, and less frequently in the younger groups, pain, both spontaneous and induced by pressure, may occur in the adipose tissue. It seems that tender areas may precede the development of lipoma-like deposits. Case I, described above, had painful adiposity and frequent mysterious attacks of pain in various locations. In one of these attacks her appendix was removed at another hospital. In the skin we have noted flushing, at other times mottled areas of cyanosis. Sometimes there may be purpura. Disturbances of the nervous system are not uncommon. Insanity occasionally occurs.

As to the course pursued by this group of marked adiposities, there seems to be, at least occasionally, a tendency to revert back to normal. Children with marked obesity, presumably of this type, have later seemed normal. What may be mild degrees of neurohypophyseal obesity in early adolescence is followed by normal adulthood. We have noted histories of adiposity and amenorrhea during adolescence in patients who later seemed normal and bore children. Adults with marked obesity sometimes revert toward more normal states of nutrition. We suspect that improvement attributed to endocrine therapy may often have been an illustration of the natural course of neurohypophyseal obesity.

More or less striking obesity may at times appear to be related to some specific endocrine gland. Hyperinsulinism probably gives us the best examples of so-called "exogenous"

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### THE TREATMENT OF PITUITARY INSUFFICIENCY AND PITUITARY HYPERFUNCTION

#### HYPOPITUITARISM

IN spite of the great advance in our knowledge of pituitary anatomy and physiology the treatment of clinical disorders of the gland is far from satisfactory. The reasons are numerous.

Recent studies of the pituitary have demonstrated the complexity of its action. The number of separate effects suggested by physiologists is so great as to lead to actual confusion. In one or other of the many laboratories in which investigations are now being made, growth, thyrotropic, adrenotropic, galactagogue, ketogenic and diabetogenic fractions have been prepared. This list does not include the gonadotropic or sex-stimulating hormones of which three with definite and distinct actions have been suggested nor does it take account of the substance obtained from pregnancy urine which has been variously named prolan, antuitrin S and follutein and which has an action quite similar to one of the gonadotropic hormones of the pituitary.

None of these extracts is entirely protein free and each potent fraction exhibits to a greater or less extent more than one effect. For instance, most of the extracts thus far obtained, whether designed to exert growth, thyrotropic or galactagogue action, appear to have some diabetogenic activity.

cases sugar, bread and potatoes may be excluded. In other words, one is approaching caloric starvation without protein starvation. Patients may be taught to make a bread substitute, such as low-carbohydrate, fat-free bran muffins. Great pains are necessary in instructing the patient and in obtaining perfect cooperation. With less extreme types of obesity and as reasonable weight is approached, the diet may be more liberal.

In a discussion of endocrine obesity one should note that lipomatosis of varying degree may be observed in different types of endocrine disease. Lipomatosis may be accompanied by more or less marked constitutional symptoms. Nervous manifestations are sometimes prominent. Insanity may complicate the picture. Menstrual disturbances frequently occur. Sometimes the development of these fatty tumors seem related to the menopause. There are rare conditions of diffuse symmetrical lipomatosis. They are usually suspected of being "endocrine" in origin. The bizarre deposits usually occur above the level of the girdle. Sometimes they are confined to the cervical region. With these conditions, the remainder of the body may be surprisingly thin.

Concluding, let us suggest that the great majority of cases considered endocrine obesity do not fall into groups of distinct, clearly defined entities but are variants of a common morbid process. Differences in the age of onset, in inherited constitutional factors together with fluctuations of various neuro-endocrine influences result in extremely varied clinical pictures.

even among individuals of the same species. Thus the demonstration that a particular preparation will exert important physiological actions in a laboratory animal is not sufficient evidence to indicate that it will accomplish similar effects in man. Even when two species are similarly affected, the required dosage may vary widely. Relative weights offer no valid criterion for estimating the amount to give.

In all available animals the pituitary gland is so small and the yield of active material is so slight that commercial extracts have a prohibitive cost. Assuming equal sensitiveness of species, the relatively small amounts which may be physiologically effective in a rat must be multiplied several hundred times to accomplish the same action in man. It has been calculated with one of the best so-called "growth" extracts that it would be necessary to administer a daily dose of approximately 50 cc. in order to accomplish in a small man the effect which can be demonstrated so dramatically in laboratory animals.

Not the least of the factors which have delayed effective replacement therapy in man are the relative rarity of well-marked and accurately recognizable cases of pituitary insufficiency and the delay in establishing definite criteria by which to identify pituitary participation in borderline conditions. Even in the advanced cases, our methods for evaluating clinical action of extracts are crude and inexact and it is quite possible that in some instances beneficial effects of active hormones are entirely missed while in others favorable psychological response on the part of the patient may lead the physician to unjustified optimism.

At the present time the list of pituitary preparations commercially available is long, the nomenclature adopted by the various manufacturers is confusing and the claims are extraordinary and in many instances absurd. Some products are almost or entirely inactive: others have an activity sufficient to produce effects in small animals but are so weak as to exhibit no clinical benefit in the doses which are recommended and economically feasible. A few preparations pro-

The most carefully prepared galactagogue hormone may influence growth and may possess maximum adrenotropic potency. Gonadotropic fractions may not be free from thyrotropic effects.

Hypophyses of different species do not contain the same amount of each hormone. Thus identical methods of extraction when applied to the glands of different species will yield grossly different products. Even when glands of a single species are employed standardization is imperfect and it is probable that all available preparations have wide variations in potency.

Antagonism and synergism between different pituitary hormones have been insufficiently studied but are probably of importance. Thus there is considerable evidence that growth and gonadotropic hormones are to some extent antagonistic in such a way that an excess of growth stimulus may inhibit sexual development, an effect evident in the genital hypoplasia of prepubertal gigantism and in acromegaly and also perhaps in the slowing of growth which occurs with rapid sexual development at puberty. It has also been shown that fractions prepared with the idea of eliminating all influences except the growth stimulus have actually less potency in promoting growth than others which are less purified. Recently it has been demonstrated that both thyrotropic and galactagogue hormones either possess separate growth-promoting effects or else act as synergists to a hypothetical pure growth hormone.

Collip's demonstration of the so-called "antihormonal" effect which develops with the continued use of many pituitary preparations introduces another practical difficulty in therapeutic application. The nature of this phenomenon is still in dispute, present evidence indicating that it may be due to a reaction from the protein contained in most pituitary extracts rather than to the development of a true antihormone. Whatever may be its explanation, the fact remains that with many of the preparations now available, the initial and desired effect is later neutralized or reversed by continued treatment.

The effect of extracts varies widely in different species and

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per cent, phosphorus 4.3 mg. per cent. A sugar tolerance test was normal.

The state of pituitary cachexia which follows destruction or ablation of the anterior lobe of the hypophysis was first described in man by Simmonds. It is regularly accompanied by a secondary atrophy of the genitals, the thyroid and adrenals and to a somewhat less degree by wasting of all tissues of the body. Clinically it is characterized by undernutrition, muscular atrophy, hypoplasia of the genitals, amenorrhea, a basal metabolic rate at the myxedematous level, and by low blood pressure and easy fatigue, features which have been attributed to adrenal insufficiency.

Although cases of complete destruction of the anterior lobe of the hypophysis are rare, many patients are encountered who present several of the symptoms of Simmonds' disease to a more or less striking degree and who must be considered as possible examples of pituitary insufficiency.

In the case of the girl who has just been presented, the criteria for positive diagnosis are not well established. Amenorrhea brought her to the clinic. Examination revealed moderate emaciation, easy fatigue, hypotension, a low basal metabolism, hypoplasia of the genitals. In the absence of chronic infection or other serious organic abnormality, the diagnosis of pituitary insufficiency may be justified.

From the circumstances of the case it may be inferred that the pituitary insufficiency was not apparent during childhood or at puberty and also that at the time of our observation it was not complete.

The girl was of normal height, the breasts while small had developed normally, the hair of the body had appeared in the normal female distribution. The menses had started rather late but appeared to be normal for eighteen months.

The weakness was not so extreme as to prevent ordinary occupation. A persistent cycle of uterine changes was indicated by the recurrent periodic cramps. The blood pressure while low did not reach those levels which frequently cause incapacity in complete pituitary cachexia. There was

duce demonstrable effects in amounts sufficiently small to be clinically practical. At least one available extract contains thyrotropic principle in amounts sufficient to produce measurable and at times striking changes in the metabolic rate. Several pituitary preparations have a sex-stimulating effect in monkeys and if judged from preliminary and somewhat meager clinical observations appear to produce similar changes in women. It would appear that these might be helpful in states of pituitary insufficiency particularly in those cases in which hypofunction of the thyroid with low basal metabolic rate and in those in which sexual infantilism are found to exist.

The circumstances of the following case give a fair example of the difficulties in diagnosis and in treatment.

**Case I.**—G. W., an unmarried woman of twenty-seven, was first seen in the Washington University clinics in June, 1935. She complained of amenorrhea for seven years and stated that for about two years she had suffered from easy fatigue. In spite of this she was able to keep her position as a dictaphone operator and to aid materially in the support of her family. As a child she had had only measles and chickenpox. Her menses had started at the age of fifteen, were regular for the first eighteen months, gradually became irregular and scanty and stopped completely when she was twenty. Following their cessation, she had periodically each month headaches and abdominal cramps. At times but not regularly she noted some secretion from her breasts. She had never experienced any sexual desire.

Physical examination revealed a somewhat malnourished girl, 65 inches in height and weighing 104 pounds. Her skin was smooth and only moderately wrinkled. The axillary hair was sparse, the pubic hair normal. Her breasts were small but had a normal amount of glandular tissue. The systolic blood pressure was 95, the diastolic 65. Gynecological examination showed an infantile uterus with small adnexa. The basal metabolic rate was  $-21$  per cent.  $x$ -Ray of the skull revealed a normal sella turcica. Serum calcium was  $11.2$  mg.

This pituitary preparation is known through the studies of Thompson<sup>1</sup> to possess among other properties a thyrotropic action in man and will in most cases cause a demonstrable effect upon the basal metabolic rate. For four weeks she received daily doses of 2 cc. The effect is best judged by reference to the table. The first notable action was a rise in basal metabolic rate followed after a brief interval by a definite fall to values well below those which preceded treat-



Fig. 23—Case I showing the myxedematous puffiness of the face which appeared for the first time following the administration of a pituitary extract possessing thyrotropic qualities.

ment. This secondary effect was not unexpected, had been noted repeatedly by others and should be considered an example of the so-called "antihormonal" effect.

It was remarkable in this case that during the period of falling basal rate, the patient acquired for the first time the appearance of myxedema with increased dryness of the skin, swelling of the face and marked puffiness under the eyes. Curiously these changes in appearance and in basal were re-

no history of sudden weakness with gastro-intestinal symptoms, an occasional feature of Simmonds' disease which simulates closely the addisonian crisis.

Many of the symptoms of this case, low basal rate, low blood pressure, amenorrhea, and weakness are observed in uncomplicated hypothyroidism. Although this was not thought to be the correct diagnosis, she was given 0.06 Gm. of thyroid daily from August 1 to September 5, 1935, and 0.03 Gm. until September 10. The effect of this treatment was to produce elevation of the basal with slight increase in blood pressure but without causing return of the menses and without subsidence of fatigue.

Immediately after discontinuance of thyroid medication her basal dropped again as may be seen in the accompanying table. In October, 1935, treatment with *phyone*\* was started.

TABLE 1  
EFFECT OF TREATMENT UPON WEIGHT, BASAL METABOLISM AND BLOOD PRESSURE IN CASE I

Date	Weight	Basals	B.P.	Remarks
July 25, '35	104	-21		
Aug. 1	105	-18	90/55	Thyroid 1 grain started
Aug. 15	108	-4		
Sept. 5	109	+14	100/60	Thyroid $\frac{1}{2}$ grain
Sept. 10	108		108/75	Thyroid discontinued
Sept. 17	110		95/60	
Oct. 4	109	-23	90/70	Phyone 2 cc. started
Oct. 11	108	-15	85/55	daily
Oct. 17	109	-28		
Oct. 24		-37		
Oct. 30	110	-34	85/55	
Nov. 7	112	-28		Phyone discontinued
Nov. 21	111	-39		Myxedematous appearance noted
Dec. 3	108	-17		
Dec. 24	111	-24		
Jan. 20, '36		-19		Prephysin 1 cc.
Jan. 26				Prephysin discontinued
Jan. 29		-35		
Feb. 11	109	-35	108/60	
Feb. 28		-35		
March 16			110/70	Prephysin 1 cc.
March 22				Prephysin discontinued
April 4				

\* Phyone was supplied to us through the courtesy of Dr. David Klein of the Wilson Laboratories, Chicago, Ill.

tumors of the eosinophile cells of the anterior lobes and giving rise either to prepubertal gigantism or acromegaly; the second, pituitary basophilism, recently emphasized by Cushing as an accompaniment of the relatively rare tumors of basophile cells. Tumors of the chromophobe cells of the hypophysis, clinically more numerous, produce no recognizable endocrine disturbance. Although it is not unlikely that states of hyperpituitarism result from physiological overactivity of cells without tumor formation, the contention is not at present susceptible to clinical or pathological proof.

Treatment of hyperpituitarism is limited at the moment to surgical removal of the tumor or to irradiation of the pituitary region. In acromegaly, operations have frequently been necessary because of the size of the tumor and its pressure upon the optic nerves or other neighboring structures. In many instances, such treatment has been successful in preventing further advance in the deformities of the disease.

In most cases of pituitary basophilism the tumor has been small. In only one instance has such a tumor been removed by operation. This was in the case reported by Lissner<sup>2</sup> at the meeting of the Association for the Study of Internal Secretions in 1936. In his patient were found characteristic changes of the syndrome described by Cushing. Operation was performed and a tumor having indifferent staining qualities and apparently arising from the pars intermedia of the gland was removed. Immediately improvement followed with regression of the prominent features of the disease for a period of two years.

While in acromegaly and possibly in cases of pituitary basophilism, it is possible to stay the progress of the condition by surgical means, the dangers of the operation are considerable. Furthermore, the approach is difficult and the tumor cannot often be sharply separated from the gland in which it is imbedded. As a result, the hypophysis itself has in many instances been destroyed with subsequent development of pituitary cachexia. Such considerations emphasize the hope of other forms of therapy.

accompanied by any variation in her subjective feelings. The last injection of *phyone* was given in November and was accompanied by a rather severe local reaction. Following its discontinuance, there was an elevation of the basal metabolic rate to levels approximately those observed before *phyone* was given.

In January, 1936, it was decided to try the effect of *prephysin*, a preparation of the Chappell Laboratories, said, on the basis of extensive laboratory investigation, to contain relatively large amounts of the gonadotropic hormone of the hypophysis. One cc. of this substance was given subcutaneously for six successive days. Again the basal metabolic rate fell but there were no other evidences of effect. The same course of treatment with *prephysin* was repeated in March, 1935, but was also without effect. Examination revealed no change in the size of the uterus. Menses were not induced although the patient continued to note the periodic return of cramps and headaches each month.

In this case, two pituitary extracts were employed. Each was prepared under excellent auspices; each had been found to have predictable actions in laboratory animals. The first preparation, *phyone*, produced notable but unfavorable changes; the second had no demonstrable effect, except a fall in the basal metabolic rate which from previous laboratory tests was not expected.

This experience does not necessarily imply that the extracts were clinically worthless. It does not preclude the cautious trial of these and other carefully prepared pituitary products. It illustrates a few of the difficulties which at the present time are inevitably encountered whenever the treatment of hypophyseal insufficiency is undertaken. It indicates the necessity of great numbers of careful clinical observations on the newer and well-tested laboratory products.

#### HYPERPITUITARISM

Overactivity of the pituitary gland finds clinical expression chiefly in two forms: the first, associated regularly with

large: 3 of his brothers being over 6 feet tall and weighing 200 pounds. He was small until the age of fourteen or fifteen, when he measured about 65 inches and weighed 125 to 130 pounds. At the time of administration his weight was 218 pounds and he was 74 inches tall. He had noted some growth in the size of his head in the preceding two years, and also a change in his facial expression. There was no loss of weight, no failure of libido, no disturbance of vision. At the time of entry he wore size 11 shoes. Three years before he had worn size 9.

Physical examination showed a man of large stature, with the heavy frame, large feet and spadelike hands. His face was large, the nose enormous, the eyes deep-set with large frontal prominences. He had marked mandibular prognathism. The general examination revealed no abnormalities. Laboratory studies showed a normal urine, normal blood count and negative Kahn. The glucose tolerance test was of diabetic type. The basal metabolic rate was plus 3.  $x$ -Ray of the skull showed a greatly enlarged sella turcica especially in the anterior posterior diameter. The neurological examination was entirely negative. Visual fields and ocular fundi were normal.

On December 3 and 4, 1934, he received two  $x$ -ray treatments directly over the pituitary region. This produced no unfavorable reaction and caused abrupt cessation of his headaches. On January 17, 1935, he received a second course of deep  $x$ -ray therapy. By March, 1935, his headaches had returned, although they were not so severe as those he had experienced before treatment. The third course of two  $x$ -ray treatments was given on March 4 and 5, 1935. Because his headache was little influenced by the third course he had a fourth treatment on June 12 and 14. This time he had a rather severe reaction to the  $x$ -ray.

Since headaches of variable severity continued during the summer he was admitted in September to the hospital with the idea that operation might be necessary. With bed rest he



As early as 1909, Granezma<sup>3</sup> of Turin reported the case of a woman forty-five years of age who suffered from the severe headaches of acromegaly. By irradiation with  $x$ -ray he was able twice in eight months to cause the headaches to disappear. Unfortunately he was unable to save the life of his patient.

Detailed study of the effects of  $x$ -ray may be said to have started with the work of Beclere,<sup>4</sup> who reported his first experiences in 1913. Especially significant was his account of an acromegalic girl with severe headaches, dizziness, vomiting and serious visual disturbances. She showed some evidences of gigantism as well as sexual infantilism. Improvement of her subjective symptoms started within fourteen days of the first irradiation. One year later the headaches and dizziness had entirely disappeared and the visual disturbances, of which Beclere made careful observations, had improved. Since that time many observations have been made on this form of therapy. An idea of their extent may be obtained from the report of Pfahler<sup>5</sup> who in 1931 was able to find that good results from the roentgenological treatment of pituitary tumors had been reported by at least 77 authors. Recent reports of significance have been made by Pfahler<sup>6</sup> on the careful study of 21 cases of pituitary tumor, 9 of which were acromegalic, and by Perémy<sup>7</sup> who assembled 97 cases, of which 35 were acromegalic. At present it is the consensus that irradiation of eosinophilic tumors of the hypophysis offers definite hope of improvement. The results in the literature indicate a wide variation in effect, a part of which may be explained by differences in technic and a part possibly to differences in the resistance of tumor cells.

**Case II.**—H. S., a farmer, twenty-one years of age, was admitted to Barnes Hospital November 26, 1934. For nine months he had suffered from occipital headaches radiating to the temporal regions. For a month he had noted nocturia and frequency of urination.

He gave the history that all members of his family were

means at our disposal in the treatment of states of hyperpituitarism it must be emphasized that neither represents an ideal form of therapy. Some interest attaches to recent experiments, particularly those of Barnes<sup>14</sup> and of Nelson<sup>15</sup> who advance evidence that an excess of ovarian hormone may cause temporary arrest of at least one of the functions of the gland. The influence of the hypophysis upon other glands of internal secretion has been established by numerous investigations in the past few years. More recently, the effect of other glands upon the activity of the pituitary has become increasingly evident. The hope, therefore, may be entertained that, eventually, hyperfunction of the hypophysis can be influenced by factors other than removal or destruction of tumors.

#### SUMMARY

There is great need for clinical study of the treatment of diseases of the hypophysis. Although in states of pituitary insufficiency, replacement therapy should be effective, the present use of extracts is surrounded with many difficulties. Experience in laboratory animals cannot be applied directly to man and advance in therapy can come only from meticulous clinical observations under well-controlled conditions.

Hyperpituitarism in its recognized forms of gigantism, acromegaly and pituitary basophilism can in many instances be controlled either by operation or irradiation.

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became so much more comfortable that operation was deferred.

In December he was seen again suffering from headaches of maximum severity. Advice for further  $x$ -ray treatment was not followed, but in May, 1936, the headaches had disappeared completely.

It is particularly notable that from the time of the first treatment there was no demonstrable advance in the acromegalic deformities.

The results of treatment in this case while not dramatic confirm the impression of many observers that irradiation may be helpful in controlling symptoms and in staying the progress of the disease. That the effect of  $x$ -ray should be tried in all acromegalic patients whose vision is not immediately threatened seems evident.

Experience with irradiation in cases of pituitary basophilism has been extremely limited.<sup>8, 9, 11</sup> The improvement observed in a few might lead to the hope that basophile cells are more vulnerable to the  $x$ -ray than are the cells of eosinophile tumors. Particularly notable was the result obtained in a case originally observed by Cushing<sup>10</sup> and reported this year by Aub<sup>11</sup> at the Association of American Physicians. Following irradiation this patient showed immediate and dramatic improvement with eventual complete regression of symptoms and return to normal configuration.

Accumulating evidence indicates that symptoms clinically indistinguishable from pituitary basophilism accompany and apparently may be produced by adrenal tumors. In a few of these cases careful serial sections of the hypophysis at autopsy have revealed no abnormality. In the individual case observed clinically the possibility of adrenal disease must always be considered. At present, it is not demonstrated that irradiation of the pituitary would be beneficial under such conditions. It is, therefore, not surprising to find in the literature cases of Cushing's syndrome in which no helpful effect from  $x$ -ray was obtained.<sup>12, 13</sup>

While at present operation and irradiation are the only

## CLINIC OF DR. LOUIS F. AITKEN

### BARNES HOSPITAL

#### DIAGNOSIS AND TREATMENT OF HYPERINSULINISM

HYPERINSULINISM may be defined as a condition in which repeated hypoglycemic attacks result from the production of insulin in excess of the physiological needs. Although Harris<sup>1</sup> introduced the term only two years after the discovery of insulin<sup>2</sup> it was not until 1927 that Wilder<sup>3</sup> first described the clinical condition. He reported the case of a physician who had a carcinoma of the islet tissue of the pancreas with metastatic growths in the liver. In the nine years that have elapsed since Wilder's report the literature has become voluminous.<sup>4</sup> Many cases have been recorded and the dramatic results which may be obtained from correct diagnosis and operative removal of a tumor of the islands of Langerhans have been well established.

The following case illustrates many of the features by which the diagnosis may be determined and also indicates some of the problems that have arisen in the study of this fascinating condition.

**Case Report.**—E. M., a married woman of forty-four, entered Barnes Hospital on June 19, 1933. Her illness began in the summer of 1929 at which time there were symptoms of nervousness and attacks of confusion, amnesia, automatism and unconsciousness occurring before breakfast, and quite similar to attacks later identified as hypoglycemic in origin. In August, 1929, she was said to have had a classical picture of Graves' disease with a basal metabolic rate of  $+80$  per cent. After preparation with iodine and quinine a subtotal

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one to two minutes by intravenous administration. Fasting true blood sugar values of 10, 22, 34, 29, and 15 mg. per cent were noted at various times during her study. A sugar tolerance test of 1.75 Gm. of glucose per kilogram of body weight gave the following results:

Fasting sugar	10 mg. per cent
$\frac{1}{2}$ hour	106 " " "
1 "	179 " " "
2 hours	248 " " "
3 "	228 " " "
4 "	124 " " "
5 "	60 " " "
6 "	39 " " "
7 "	37 " " "
8 "	45 " " "
9 "	47 " " "

During the fourth hour of the test she developed a severe headache and hunger followed by vomiting. During the fifth hour she became confused and her facial expression was blank and staring. She responded to questions and commands, but had complete lapse of memory for all events which followed the headache and vomiting.

On a carbohydrate intake of 150 Gm. supplemented by 200 cc. of orange juice at 3 A. M., the following blood sugar values were obtained: 6 P. M., 72; 9 P. M., 34; 12 M., 43; 3 A. M., 24; 6 A. M., 42; 9 A. M., 81; 12 M., 55; 3 P. M., 83; 6 P. M., 84. The blood amylase test was normal by Somogyi technic. Basal metabolic rate was -6 per cent. The blood Kahn was negative. Stereo of skull and other laboratory findings were within normal limits.

At the time this patient was being studied, the work of Houssay, Barnes<sup>5</sup> and others had shown that many extracts of the pituitary gland contain a diabetogenic principle which tends under some conditions to raise the level of blood sugar. A study of the effect of such an extract on a patient with hyperinsulinism appeared to be of some interest. She was given therefore a pituitary fraction, Q 40, which was furnished to us by Dr. J. B. Collip. This was administered in doses of

thyroidectomy was performed. Except for a gain in weight her convalescence was uneventful. Previously noted fibroids were satisfactorily removed in April, 1930. By June of that year she had again developed attacks of confusion, weakness, clumsiness, and at times unconsciousness and convulsions.

Milder manifestations were a sense of inward nervousness, at times hunger, mental confusion, disorientation, purposeless or athetoid movements, muscular twitchings, and repetition and thickness of speech. There were many phases of prolonged amnesia and automatism. During one such attack she telephoned a physician, admitted him to her household, and then proceeded to roll violently across the floor from one side of the room to the other. A sharp command arrested the activity so dramatically that a diagnosis of hysteria was made. In March of 1933 after a prolonged series of convulsions a right-sided hemiplegia developed. She remained unconscious and hemiplegia persisted for four days in spite of generous amounts of intravenous glucose. With return of consciousness the hemiplegia disappeared. Blood sugar studies and a five-hour sugar tolerance revealed a diabetic curve without hypoglycemia. The attacks gradually became more frequent and increasingly severe. Characteristically they would develop after a prolonged fast or following unusual physical exercise.

Her husband learned early in the course of the patient's illness that sweetened milk would alleviate mild attacks and abort an attack of unconsciousness. In June, 1933, attacks were frequent and severe. She herself learned that if she would eat a hot dog sandwich and drink a bottle of beer at midnight, she could avoid a convulsion the following morning.

Physical examination revealed obesity, a coarseness of features with some lack of expression; a moderate hypertension, 150/90, and the scars of thyroidectomy and hysterectomy. The neurological examination was entirely negative. During hospitalization in June, 1933, many attacks were observed. Prompt relief of symptoms could be induced in fifteen to twenty minutes by ingestion of carbohydrate, and in

consistency, attached to pancreatic tissue. It appeared to be partially encapsulated. Sagittal section disclosed a necrotic area,  $4 \times 3$  mm., eccentrically placed. The tumor was divided into small pieces for fixation in aqueous chrome sublimate and modifications of the same containing 10 per cent formalin and 5 per cent acetic acid respectively, Bouien's and Altmann's fluids, and 10 per cent formalin in 90 per cent alcohol. Bits were also placed in Ringer's fluid and in 1:2000 neutral red in normal saline for examination in the fresh state.

The fresh material did not tease readily and cells for study were obtained with difficulty. These were examined with the oil immersion lens. Their cytoplasm showing a haze of tiny granules characteristic of the cells of normal islets of the pancreas, and a variable content of refractile globules suggesting lipoid. The nuclei were large, clear and contained a prominent nucleolus. In the fresh material previously immersed in neutral red, the granules of occasional cells stained with the dye, those of the majority, even when adjacent to cells with colored granules, remained unstained. In the cells of normal islets under similar conditions, the specific cytoplasmic granules color with the dye. Macrophages, mast cells and lymphocytes in considerable numbers were observed in addition to the cells heretofore described.

The fixed material, after dehydration and embedding, was sectioned in paraffin at 4 microns and stained with Heidenhain's azocarmine modification of Mallory's connective tissue stain, Bensley's and Bowie's neutral stains, and hematoxylin and eosin.

Figure 24, *a* and *b*, are low-power photomicrographs of areas of the formol chrome sublimate block of the tumor stained with hematoxylin and eosin and the modified Mallory stain respectively. Examination of these sections revealed that the tumor was composed of cords and irregular masses of cells closely akin to the cells found in normal islets of the attached pancreas. In places, the tumor tissue encroached upon normal pancreas (Fig. 24, *b*): and lobules of acinar tissue were observed to project into the tumor and cords of tumor cells across



2 cc. every three hours for twenty-four hours. A sugar tolerance test following the last injection failed to show any appreciable change in the character of the curve. It may be mentioned in passing that the conditions of this trial were not favorable, that the potency of the fraction in diabetogenic principle was not definitely known and that the duration of administration may not have been sufficient. This observation does not preclude the possibility that other extracts with greater diabetogenic action given under other conditions might not have a demonstrable effect. At the time the condition of the patient did not permit further observation of this type of therapy.

On June 29, 1933, following the administration of 500 cc. of intravenous glucose, Dr. A. O. Fisher using avertin and nitrous oxide anesthesia explored the region of the pancreas. The abdomen was opened through a left paramedian incision. There was a very thick layer of fat in the abdominal wall. The rectus was retracted laterally, the peritoneum was opened and the gastrocolic omentum was incised, affording a rather good exposure of the pancreas which lay deep in the wound. The posterior parietal peritoneum was incised over the pancreas and it was possible to palpate the latter throughout its entire length and even to the head. Nothing was made out on inspection, but about the middle of the body of the pancreas a firm well-defined area quite different from the normal pancreas was felt. Assuming that this area contained the tumor, it was removed, taking a wedge-shaped portion of pancreas. After removal it appeared to be more like an isolated island of firm tissue. There was considerable troublesome bleeding which was carefully controlled. The cut edges of the pancreas were approximated with interrupted sutures. The field was left quite dry and a Penrose drain was brought from this region through a stab wound in the left side.

Dr. James O'Leary examined the tumor and made the following histological study:

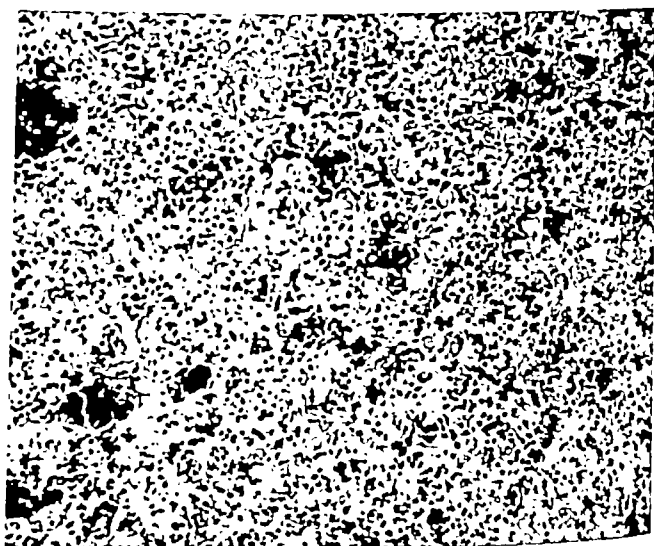
Inspection of the material revealed a small ovoid tumor. 13 × 6 mm. in size, yellowish gray in color, of firm elastic

consistency, attached to pancreatic tissue. It appeared to be partially encapsulated. Sagittal section disclosed a necrotic area,  $4 \times 3$  mm., eccentrically placed. The tumor was divided into small pieces for fixation in aqueous chrome sublimate and modifications of the same containing 10 per cent formalin and 5 per cent acetic acid respectively, Bouien's and Altmann's fluids, and 10 per cent formalin in 90 per cent alcohol. Bits were also placed in Ringer's fluid and in 1:2000 neutral red in normal saline for examination in the fresh state.

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a



b

Fig. 24.—*a*, Low-power photomicrograph of a typical area from the tumor; *b*, low-power photomicrograph of a zone in which the tumor adjoins normal pancreatic tissue. *Ad*, Adneoma; *Pad*, pancreatic tissue.

the boundary into acinar tissue. In other areas the normal pancreatic and the tumor tissue were separated by a mass of

somewhat hyalinized connective tissue containing ducts, ducts apparently differentiating into tumor cells (Fig. 25), and lobules of acinar tissue.

The larger area of the tumor was representative of the early and intermediate stages of Bensley's chronological classification of islet cell adenomata (Womack, Graham and Gnagi, 1931).<sup>6</sup> The cords and small masses of tumor cells were separated by capillary vessels of varying width. The amount of connective tissue about these varied from very slight to a

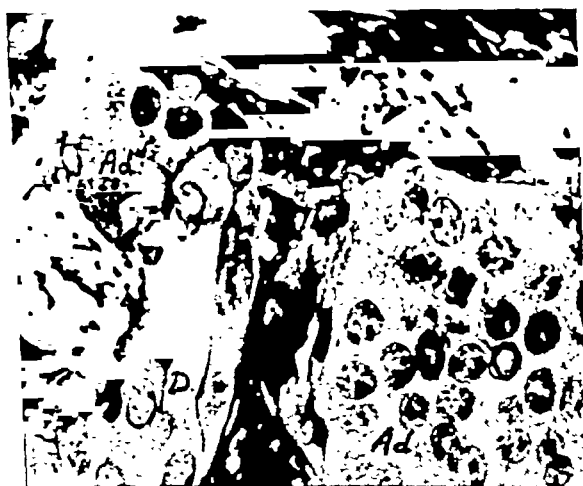


Fig. 25.—High-power photomicrograph of a zone centrally situated in the tumor illustrating the differentiation of a duct into adenomatous cells and a typical group of islet tumor cells. *D*, Duct; *Ad*, adenomatous tissue.

small amount. In a few small areas, an approximation of the older stage of Bensley's classification, in which cords of islet tissue were separated by strands of hyalinized connective tissue was observed.

The tumor cells were on the whole slightly larger than the normal islet cells in the adjoining pancreas; but the same shape variations were evident (Fig. 26). In large areas the majority of cells appeared healthy, few pyknotic nuclei being observed; in other areas pyknotic nuclei were much more frequent, the cytoplasm of many cells was pale (H. and E.). In

the latter cells characteristic cytoplasmic granulations were absent and cell boundaries not distinct.

The staining reactions of the majority of healthy tumor cells resembled those of the beta variety of normal islet cells (control: islets of adjoining pancreas), but differences were evident. After formol chrome sublimate fixation, the specific granules in the beta cells of normal islets colored faint blue with the modified Mallory stain; the tumor cell granules which varied somewhat in size, colored a dull lilac. Whereas in normal islet beta cells the cytoplasm in which the granules

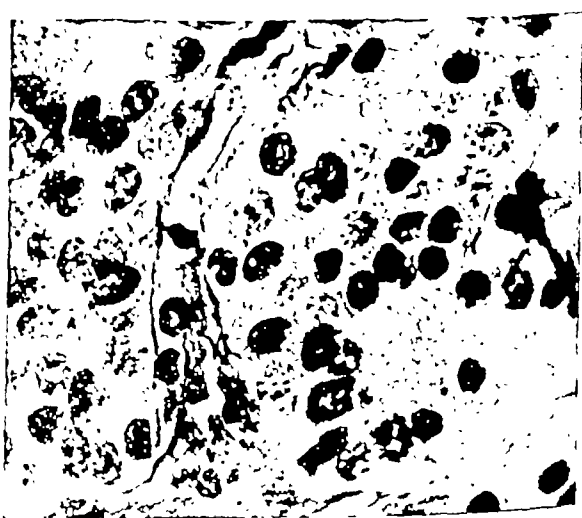


Fig. 26.—High-power photomicrograph illustrating the occurrence of degenerative cells in an area still containing healthy cells.

were embedded failed to stain, in the tumor cells it colored the same as the granules but less intensely. Material fixed in aqueous and acetic chrome sublimates gave similar deviations in the staining reactions between normal islet beta cells and the cells of the tumor. A small minority of healthy appearing cells in the tumor (formol chrome sublimate) had specific cytoplasmic granules which, like those of the  $\beta$  cells of normal islets of the pancreas, colored an intense blue with Bensley's neutral gentian. These may represent true  $\beta$  cells.

Other differences were apparent between the islet and the

tumor cells. Many tumor cells possess the characteristic cytoplasmic inclusions of varying shape and staining bright red with the modified Mallory stain. These have been observed in variable numbers in each of the other four tumors<sup>7</sup> of similar nature removed at Barnes Hospital. They have not been found in normal islet cells. An occasional cell occurred in the tumor, the cytoplasm of which was loaded with vacuoles of uniform size; these cells are to be distinguished from cells bearing one or more small vacuoles which occur in normal islet and in tumor islet tissue alike.

The similarity in size of the cytoplasmic granules of tumor islet cells and those of argentaffine cells of the gastro-intestinal tract, which may also form tumors, make it necessary to rule out the latter. This was accomplished by a specific staining reaction for the granules of argentaffine cells discovered by Masson (1928).<sup>8</sup> The granules of the tumor cells did not stain with the silver, whereas excellent stained granules were obtained in the argentaffine cells of a control section of intestine.

The paucity of mitotic figures and high degree of differentiation of the component cells of the tumor discounts malignancy and, with the other evidence presented, places the tumor as a modified  $\beta$  cell adenoma of the pancreas.

Postoperatively there was a temporary period of diabetic state with fasting sugars of 248 to 255.

A sugar tolerance test fifteen days following operation was as follows: fasting, 85; half hour, 215; two hours, 218; three hours, 218; four hours, 164; five hours, 109. Subsequent to the operation the patient developed a pancreatic cyst which required drainage and marsupialization.

Gradually the patient developed symptoms of hypothyroidism with a basal of —18 per cent, and now requires  $1\frac{1}{2}$  to 2 grains of desiccated thyroid per day. At no time has there been any evidence of return of hypoglycemia.

**Discussion.**—The case illustrates many typical features of hyperinsulinism secondary to an islet cell adenoma of pan-

creas and cured by successful removal of tumor. Repeated blood sugar observations during various attacks revealed there was no direct relationship between sugar level and the severity of the symptoms. The persistent unconsciousness and hemiplegia for four days, even though generous amounts of glucose were administered and blood sugar remained at normal and hyperglycemic levels, occurred after a rather prolonged and severe attack of hypoglycemia before sugar was administered. This case as many others had been considered as hysteria, epilepsy and encephalitis.

**Symptomatology of Hyperinsulinism.**—The diagnosis of hyperinsulinism depends on the demonstration of chronic hypoglycemia dependent upon an overactivity of the island cells of the pancreas. The history of the attacks and the symptoms produced are in no way different from an overdose of insulin such as one might encounter in the treatment of diabetes mellitus. The disease is usually insidious, attacks being at first mild and occasional, later becoming more frequent and more severe. The mild attacks may be described as a feeling of weakness, hunger and nervousness. Instead of hunger the patient may complain of a feeling of heaviness in abdomen, nausea, or a rather pronounced epigastric pain. Early in the attack there is loss in ability to concentrate. The patient may feel light-headed and giddy. Emotional instability may become manifest. This may be followed by manifestations of hyperadrenalemia. The pulse becomes quickened, there is tremor of fingers and hands, blood pressure is elevated and profuse sweating ensues. Weil<sup>o</sup> calls particular attention to the finding of a circumoral pallor occurring early in the attack. If the degree of hypoglycemia progresses further there is usually some mental confusion. The patient may show long periods of amnesia and automatism. This state has often led to such erroneous diagnoses as hysteria. The patient may be hyperexcitable during this stage and undergo extremely vigorous efforts, very often with a feeling of attempting to escape from some fear or injury. Convulsions either of jacksonian or general type are frequent and

indistinguishable from true epileptiform seizures. Following the hyperanxiety state and overactivity or convulsive seizure there usually develops a feeling of drowsiness and tendency to fall asleep.

During hypoglycemia there is a deficiency of sugar supplied to the brain. With such deprivation the patient may develop symptoms of diplopia, scotomata, hemiparesis or hemiplegia or a true epileptiform convulsion. It is significant that in prolonged attacks of hypoglycemia, the restoration of the blood sugar level is not always followed immediately by a disappearance of the neurological manifestations. The latter may require several hours or days to return to normal. Although the intelligence quotient has been reported as dramatically improved by the total relief of hyperinsulinism,<sup>43</sup> some cases show marked residual mental deterioration. Those cases in which fatalities resulted in spite of adequate administration of glucose are possibly due to so prolonged a malnutrition of brain tissue as to prevent recovery and repair. Joslin<sup>10</sup> reports this same observation in association with huge overdoses of insulin in diabetic patients.

Such neurological manifestations aborted or relieved by adequate administration of carbohydrate is more than presumptive evidence of hypoglycemia. The attacks characteristically occur after a long fast or missing of a meal. Metabolic processes which accentuate depression of blood sugar level or stimulate normal insulin production such as vigorous physical exercise are apt to provoke an attack.

**Blood Sugar Studies.**—Confirmatory evidence is the finding of a low blood sugar during a seizure with prompt relief of symptoms by the administration of carbohydrate. Although a long fast may provoke an attack, fasting blood sugar values in proved cases have been found to be normal or even elevated. The sugar tolerance test is of distinct value as a diagnostic aid. The usual amount of sugar recommended is 1.75 Gm. per kilogram of body weight. Blood samples for sugar content are taken at half-hour, one-hour, two-hour, three-hour, four-hour, and five-hour intervals. The conven-



tional three-hour sugar tolerance test may fail to deviate from the normal or may actually simulate a diabetic type of curve. The marked fall in blood sugar level may be evident only in the fourth or fifth hour.

### **Differentiation from Other States of Hypoglycemia.**

—As has been emphasized the main symptoms associated with hyperinsulinism are those of hypoglycemia, which like the opposite condition of elevated blood sugar, may arise from any one of several factors controlling the storage and utilization of carbohydrate. A loss of glycogen stores secondary to extensive disease of the liver such as carcinoma,<sup>11</sup> acute yellow atrophy,<sup>12</sup> and excess fatty infiltration of the liver<sup>13</sup> has been identified as a cause of hypoglycemia. Scheiman<sup>14</sup> in a study of 6 cases of progressive muscular atrophy reported 2 cases of hypoglycemia. A depletion of the glycogen reserves sufficient to produce very low levels of blood sugar has been observed in malnutrition,<sup>15</sup> in renal diabetes,<sup>16</sup> in lactation,<sup>17</sup> and in prolonged muscular exercise.<sup>18</sup>

Hypoglycemic reaction resulting from increased vagotonia was reported in 1926 by J. M. Nielsen.<sup>19</sup> Ryneerson<sup>20</sup> later reported 2 cases in which there was hypoglycemia associated with vagotonia which was interpreted as being secondary to psychiatric disturbances influencing the blood sugar regulating center in the pons. The antithesis of this blood sugar regulating effect is clearly demonstrated in the case of de Takáts and Fenn<sup>21</sup> in which the diabetic state of a boy with Graves' disease was much improved following thyroidectomy. His diabetes continued to be rather difficult to control and was attributed to a persistent high degree of sympatheticotonia. There was a dramatic increase in sugar tolerance following a bilateral section of the splanchnic nerves.

The loss of control of blood sugar level resulting from altered function of the other glands of internal secretion may simulate true hyperinsulinism. Adrenal insufficiency, pituitary tumors and hypothyroidism have been associated with hypoglycemic convulsions. Some of the earliest reports of hypoglycemia were found in cases of Addison's disease.<sup>22</sup>

Anderson<sup>23</sup> reports a case of fatal hypoglycemia in which a tumor of the adrenal gland was found. J. Wilder<sup>24</sup> reported a case of pituitary tumor with hypopituitarism in which severe hypoglycemic attacks were aborted only by adequate administration of carbohydrate. This has been interpreted as a loss of the diabetogenic substance of the hypophysis demonstrated by Houssay<sup>5, 25</sup> and others. The rôle of this substance is further emphasized in the Houssay dogs where total ablation of the hypophysis is accompanied by an extreme sensitivity and hypoglycemic effect to relatively minute doses of insulin.

The association of hyperglycemia and glycosuria with thyrotoxicosis is well known.<sup>26</sup> Reduction of insulin requirements and increased carbohydrate tolerance following thyroidectomy in diabetes with Graves' disease has frequently been observed. The antithesis of this relationship is cited in Campbell's<sup>27</sup> cases of myxedema with hypoglycemia in which the level of blood sugar was stabilized by the administration of thyroid medication. Womack<sup>28</sup> resected a large portion of the pancreas in a patient with attacks of hypoglycemia associated with thyrotoxicosis in which the latter state spontaneously regressed following operation. He interprets the increased activity of the thyroid as a supplementary process of glycogen mobilization in response to the state of hypoglycemia. This result is significant in consideration of the case presented in this report. In the latter instance the hypoglycemic attacks were relieved during the state of thyrotoxicosis and returned following thyroidectomy. It is also significant that a state of hypothyroidism developed following relief of the hypoglycemia by resection of the adenoma.

Having established beyond doubt the presence of the syndrome of chronic hypoglycemia, extrapancreatic influences must be excluded. The factor of depleted glycogen stores is unlikely in the absence of any clinical evidence of marked liver or muscle disease. Test with epinephrine is useful since the hyperglycemia following its administration is dependent upon sufficient amount of glycogen in the liver. Unfortunately

it is not yet clinically possible to assay accurately the blood serum or urine for changes in quantity of the pituitary hormones. If there is any question of pituitary influence the sella turcica should be x-rayed and the patient should be most carefully observed for other evidences of pituitary dysfunction. Changes in thyroid secretion should be excluded as a possible primary or secondary contributing influence. Adrenal insufficiency must be excluded. Last but possibly not least, the factor of any fundamental disturbance of the vegetative nervous system must be investigated.

Although the type of sugar tolerance curve is not definitely diagnostic, it is worthy of note that the so-called "functional" case of chronic hypoglycemia tends to display a flat curve.<sup>29</sup> There seems to be more than a possibility that in some cases of functional hypoglycemia there exists a state of insulin hypersensitivity rather than a true overproduction of insulin. Further studies of insulin sensitivity in cases of chronic hypoglycemia have been suggested by MacBryde<sup>29</sup> as an important adjunct in the differentiation between true hyperinsulinism and functional chronic hypoglycemia.

**Pathology.**—The pathological lesions of hyperinsulinism may be classified into three groups. The first includes that of malignant degeneration of islet tissue of the pancreas with or without metastases.<sup>3, 44</sup> In Wilder's case an analysis of the tumor tissue revealed a relatively high concentration of insulin-like substance. The second comprises those cases of adenoma or adenomata of islet tissue. It is this latter type of hyperinsulinism which offers the best prognosis of permanent effective cure. Terbrüggen<sup>30</sup> was the first to observe multiple adenomata in a thirty-year-old woman in which fatal hypoglycemia occurred. Both Graham<sup>31</sup> and Whipple<sup>4</sup> report a case unimproved following excision of adenomatous tumor, who were operated a second time with the finding of a second tumor nodule which on removal effected a clinical cure.

The sizes of the tumors reported vary from the size of a small pea to that of a grapefruit. As in other glandular

tumors such as the thyroid, the severity of the symptoms bears no relationship to the size of the tumor but varies directly with the degree of secretory activity of the beta type cell. The tumors are usually found in the body or tail of the pancreas where islet tissue is normally more abundant. The smaller tumors were of a purplish-red color because of their high vascular character. The larger tumors contained areas of necrosis and were more yellow in appearance. In the baseball tumor of Graham<sup>31</sup> the degenerative process was accompanied by calcification. The tumors were not always encapsulated. In a pathological study of 5 cases of hyperinsulinism with adenomata by O'Leary<sup>7</sup> the case presented in this report was considered as a transition tumor type. In some portions of the tumor there was definite encapsulation. In other areas there was no capsule and the histological picture was typical of a simple hyperplasia and hypertrophy of islet tissue.

The final analysis of a given case should include an accurate histological study of the cellular elements making up the tumor. Bensley<sup>7</sup> and his coworkers have elaborated a study of both normal pancreas and of pancreatic tumors in which an accurate differentiation of the cellular elements can be determined. This cellular study includes examination of the fresh tissue suspended in Ringer's fluid and in 1:2000 neutral red in normal saline solution for granules and lipid content as well as special staining qualities of the fixed tissue. In those cases in which such studies were carried out, the beta type cell definitely dominated the active portion of the tumor structure.

In the third group of cases there is a diffuse simple hyperplasia and hypertrophy of the islands of Langerhans. Such cases have developed from excess stimulation of islet tissue by large and frequent carbohydrate intake or prolonged hyperglycemia. Hartman<sup>32</sup> observed the case of a child who was seized with convulsions and coma following the sudden withdrawal of carbohydrate by a stern mother in her effort to preserve her winter supply of jams and jellies. The child

had been eating regularly huge amounts of jams and jellies in spite of ordinary discipline. Sudden withdrawal of this nutriment by placing a padlock on the refrigerator resulted in a severe state of hypoglycemia with convulsions. Gradual withdrawal of carbohydrate effected an uneventful recovery.

This same pancreatic response is duplicated in some reported cases of diabetes mellitus of long standing in which the chronic hyperglycemia stimulated the remaining islet tissue to hyperactivity and hyperplasia.<sup>33</sup> Some deaths in the newborn of diabetic mothers have been attributable to a state in which during intra-uterine life there is hyperplasia of islet tissue from constant hyperglycemia, and a secondary fatal hypoglycemia following birth and removal of the infant from the maternal influence.<sup>34</sup>

De Takáts<sup>35</sup> produced hypertrophy of the islets of the pancreas by ligation of the pancreatic duct. This experimental finding was duplicated by Wilder's case in which a stone was found occluding the pancreatic duct associated with hypertrophy of the islet tissue.

**Treatment.**—*Medical.*—Some of the less severe cases of hypoglycemia attacks and possibly hyperinsulinism have been relieved by a high carbohydrate intake with frequent intermediary feedings. Such therapy, however, may lead to marked obesity and a progressively increased demand for sugar. A more satisfactory dietary treatment is that recommended by Clark and Greene<sup>36</sup> in which the depressing effect of insulin stimulation is utilized in the large fat ratio intake. Patients are placed on a diet of 60 Gm. of carbohydrate, 60 Gm. of protein, and 210 Gm. of fat. Weil's<sup>9</sup> diet in so-called functional hyperinsulinism is more palatable and about equally successful. In this, 100 Gm. of carbohydrate, 60 Gm. of protein, and 250 Gm. of fat, were used.

John<sup>37</sup> has reasoned that just as excess carbohydrate may derange the mechanism of insulin production to the extent of clinical hyperinsulinism, the use of exogenous insulin given after meals before the blood sugar has an opportunity to stimulate the secretion of insulin would effect a physiologic

rest of the islet tissue. The application of this principle appeared to be effective in 3 cases. Patients were placed on a high fat diet in the proportions of 100 Gm. of carbohydrate, 80 Gm. of protein and 250 Gm. of fat. Ten to twenty units of insulin were given one-half hour after meals. After two and one-half to three months these patients were able to discontinue insulin and return to normal diet without apparent return of symptoms. It seems unlikely that such management would be effective in true hyperinsulinism from active tumors of the pancreas.

*Surgical Treatment.*—If a case can be accurately classified as hyperinsulinism of anatomic type, the treatment of choice is surgical. The operative mortality in technically good surgical hands<sup>4</sup> is remarkably low. The finding of an adenoma of islet tissue type and its successful removal will eventuate in complete and dramatic cure, the only exception being the presence of multiple tumors or malignant degeneration with metastases in which entire removal of tumor tissue is technically impossible. A detailed description of surgical technic may be found in the following references.<sup>4, 35</sup>

In the event that diffuse hyperplasia is found, subtotal pancreatectomy has afforded excellent results. Graham<sup>39</sup> resected 80 to 90 per cent of a pancreas in a one-year-old child suffering from severe hypoglycemic attacks with dramatic cure and no lasting evidence of pancreatic insufficiency. The early failures such as that of Finney<sup>40</sup> and those reported by Judd, Allan and Rynearson,<sup>41</sup> may have been more effective had a more generous removal been accomplished.

*Treatment by Radiation.*—The relief of hyperinsulinism by radiation as reported by Barrow<sup>42</sup> has all the advantages and disadvantages of such therapy to other glandular tumors. The effectiveness in a given case is extremely difficult to evaluate and since the operative mortality is small, the possibility of overlooking an early carcinoma more than compensates for the surgical risk.

There is no doubt that the so-called "non-anatomic" or functional cases of chronic hypoglycemia are a direct chal-

lenge to the internist since the understanding of carbohydrate metabolism is far from complete and such palliative procedures as subtotal pancreatectomy should be regarded as unsatisfactory. On the contrary, prolonged but unsuccessful conservative treatment may not only prevent the possibility of curing an early carcinoma but also may allow irreparable injury and degeneration of the nervous system.

**Summary.**—1. Hyperinsulinism should be differentiated from other factors or diseases capable of producing chronic hypoglycemia. A comprehensive understanding of carbohydrate metabolism will in many instances avoid the necessity of subtotal pancreatectomy as a symptomatic cure. Exploratory laparotomy is not indicated unless the case is refractory to dietary treatment or shows rapid progression of frequency and severity of hypoglycemic attacks.

2. If carcinoma is present, prolonged conservative treatment may permit metastases to occur. Frequent and prolonged hypoglycemia retards mental development and is followed by mental deterioration.

3. Failure of relief of symptoms following removal of an adenoma may be due to existence of multiple tumors or malignant degeneration with metastases.

4. A case is presented in which an adenoma of beta cell type successfully removed produced a complete cure. The study of this case demonstrates the importance of extending the sugar tolerance test to five hours. Blood sugar determinations during various attacks revealed there was no direct relationship between sugar level and the severity of the symptoms. Blood sugar observations made after a prolonged attack of hypoglycemia were found to be within normal limits without alleviation of abnormal neurological state.

5. In this case, the development of Graves' disease following inception of attacks of hypoglycemia, the increased severity of hyperinsulinism following thyroidectomy, and the hypothyroid state following removal of adenoma of pancreas indicate a possible compensatory action of the thyroid gland in hypoglycemic states.

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### ENCEPHALITIS: CLINICAL TYPES, THEIR SYMPTOMS, DIAGNOSIS AND TREATMENT

THE terms encephalitis and encephalomyelitis have appeared in the literature with increasing frequency in the last few years, but unfortunately under these names are included a wide variety of subjects entirely unrelated to each other. Accurate classification of such disorders is impossible until more is learned of their etiology and pathology, but for the purposes of this discussion, they have been grouped according to clinical manifestations as follows: (1) Toxic encephalitis—(a) idiopathic form, (b) encephalitis due to lead or arsenic; (2) epidemic encephalitis—(a) lethargic (von Economo) type, (b) Japanese "Type B," (c) Australian X disease, (d) St. Louis type of 1933; (3) acute disseminated encephalomyelitis associated with infections (postinfection encephalitis), including postvaccinal encephalitis; (4) unclassified types.

#### TOXIC ENCEPHALITIS

This term is frequently employed to designate any form of encephalitis not clearly of the epidemic type. It would probably be better, however, to limit its use to those cases of nonepidemic encephalitis not obviously associated with any of the specific infectious diseases. The etiology may be entirely obscure, or the condition may be produced by various drugs or chemicals, especially lead or arsenic.

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Page 2

Page 3

Page 4

Page 5

Page 6

Page 7

Page 8

Page 9

Page 10

Page 11

Page 12

Page 13

Page 14

Page 15

Page 16

Page 17

Page 18

Page 19

Page 20

Page 21

Page 22

Page 23

Page 24

Page 25

ner and amount as a 20 per cent dextrose solution is commonly employed.

(b) **Encephalitis Due to Lead or Arsenic.**—This condition is much better understood than the preceding since it has long been known that both lead and arsenic when absorbed by the system even in small amounts but over a long period of time, are capable of producing toxic manifestations which may involve the nervous system. Lead, moreover, can be absorbed not only through the gastro-intestinal tract, but also through the lungs or skin in sufficient quantity to produce such symptoms. Indeed, instances are reported in which burning wooden storage battery plates, heavily impregnated with lead, have produced plumbism through inhalation of the fumes, and in children, eating paint from toys and cribs or even the use of nipple shields and dusting powders containing lead have produced such manifestations. In childhood, too, lead encephalitis seems to occur with much greater frequency than in adults, and is far more serious. That arsenic may prove to be an equally serious menace to the nervous system is attested by the fact that peripheral neuritis following its prolonged use has been recognized for many years, and encephalitis, as a sequel, has been brought to the fore especially since the use of the arsphenamine compounds in the therapy of syphilis and other conditions.

The pathology of lead encephalitis is especially striking: there is a marked increase in intracranial pressure due to intense cerebral edema, often accompanied by petechial hemorrhages, focal collections of cells, and degenerative changes in nerve cells. Injury to the central nervous system may be so great as to lead to residual spastic paralysis, epilepsy, blindness, tremors and mental deterioration.

Encephalitis due to *arsenic* is less common, but is occasionally seen especially in children receiving arsenical anti-luetic treatment. There is a greater tendency to hemorrhage, but less cerebral edema and fewer permanent residual manifestations.

*Symptoms.*—Following an indefinite period of anorexia,

(a) **Idiopathic Form.**—The disease appears to be commoner in children than in adults, but its etiology and the factors which are operative in its production are entirely unknown. Moreover, opportunities for careful studies of the pathology have not been numerous enough to warrant final classification, although rather common findings appear to be cerebral congestion and edema, petechial hemorrhages, especially in the gray matter, occasional areas of round cell infiltration and degeneration of nerve cells, but without evidence of demyelination.

*Symptoms.*—The onset is usually sudden, although occasionally it may be preceded by one or two days of malaise and even slight fever. The chief complaints are headache and nausea, followed in a few hours by marked drowsiness or convulsions. Fever rarely lasts more than a few days, and is occasionally absent. Meningeal symptoms, such as rigidity of the neck and positive Kernig or Brudzinski are not infrequently present at the onset, but rarely very pronounced or persistent. There may be paralysis of one or more extremities or of the face and eye muscles, but, as a rule, these are quite transient, disappearing completely within a few days. Changes in the knee jerks, or plantar and abdominal reflexes may be observed, but vary a great deal at different times in the same patient. The spinal fluid is clear, the pressure somewhat increased, and there is a moderate increase in globulin and mononuclear cells. The course of the disease is ordinarily a brief one, recovery occurring in the majority of cases within a few days to a week or two. Residual effects are uncommon, although mental deterioration and spastic paralysis is occasionally noted. The treatment is entirely symptomatic. Lumbar puncture may relieve the headache and even the convulsions, and theoretically, at least, the intravenous injection of hypertonic dextrose or saline solution, and especially 40 per cent sucrose (cane sugar) solution would appear to be advantageous in lessening the edema of the brain and possibly sparing the nerve cells a certain amount of damage. The sucrose solution may be used in the same man-

in lead colors, because of their well-known habit of putting such things in their mouths. Once plumbism occurs, removal of the lead (*i. e.*, by producing an alkalosis or acidosis, giving parathyroid hormone, reducing the amount of calcium ingested, etc.) is probably inadvisable, because of the danger of mobilizing the lead which may have been deposited in the bones, thus intensifying the symptoms. Since the metal is relatively inert when deposited in the bones, this should be encouraged by means of the administration of lime salts and alkaline phosphates, and perhaps adding vitamin D (viosterol, etc.) to the diet. Eventually, there is then the prospect of its gradual elimination through natural channels.

Since most of the acute symptoms may be accounted for by the intense cerebral edema, treatment of the acute phase consists largely in attempting to lessen this. Intravenous injections of hypertonic dextrose, saline or magnesium sulphate have been used for this purpose, but perhaps a better preparation would be 40 per cent sucrose (cane sugar) solution, which may be used intravenously in about the same dosage as 20 per cent dextrose solution. In addition, convulsions may require the use of sedatives. Unfortunately, treatment is rarely very effective.

#### EPIDEMIC ENCEPHALITIS

(a) **Lethargic (von Economo) Type.**—Although it seems probable that this disease was first noted many years ago, to von Economo belongs the credit of again calling attention to it, in a classical description of a Viennese epidemic in 1916. Since then it has been reported from practically all parts of the world.

*Etiology and Pathology.*—The cause is unknown, although it is usually considered to be one of the diseases due to a filtrable virus. Attempts have been made to establish a relationship between this disease and the virus of herpes simplex (fever blisters) and epidemic hiccup, but this claim has never been substantiated. Nor is the manner of its spread clear, although it is assumed that exposure to "carriers" or unrecognized cases of the disease are probable factors in its



constipation and abdominal cramps, the cerebral symptoms of plumbism develop. Briefly, these consist of a change in disposition, visual disturbances, including strabismus or ptosis, change in pulse rate and somnolence and convulsions. The increased intracranial pressure may lead to projectile vomiting, increased blood pressure and choked disks. The pressure indeed may be so great as to cause separation of the cranial sutures in children. Fever is usually absent, except in the terminal phases or when other infections are present. The spinal fluid is clear, the pressure greatly increased, and the globulin tests positive, although the cell count is either normal or shows a mild increase of lymphocytes.

When confronted with the possibility of encephalitis being due to plumbism, corroborative evidence of lead poisoning should be sought. Basophilic stippling of red cells is often present, as well as the bluish "lead line" at the edge of the gums (commoner in adults than children), and more important, the roentgenographic evidence which consists of an increased zone of density at the ends of the long bones beneath the epiphyseal line. Finally, the lead may be revealed by means of a spectroscopic examination of the blood and spinal fluid, or its quantitative estimation in the feces.

*Prognosis.*—This is always very serious, the mortality being highest in patients with convulsions, but being at least 25 per cent including all types of cases. Unfortunately, residual effects (blindness, paralysis, tremors, mental deterioration, etc.) are not uncommon even when the patient survives, and since the lead is often stored in the bones in apparently recovered cases, there is always the possibility of a recurrence of the cerebral symptoms through the mobilization of the lead stored in the bones, as the result, for example, of certain infections which disturb the mineral equilibrium of the body.

*Prophylaxis and Treatment.*—Treatment being quite unsatisfactory, every effort should be made to prevent absorption of lead through prolonged contact. In children, this means especially avoidance of toys and other objects painted

in lead colors, because of their well-known habit of putting such things in their mouths. Once plumbism occurs, removal of the lead (*i. e.*, by producing an alkalosis or acidosis, giving parathyroid hormone, reducing the amount of calcium ingested, etc.) is probably inadvisable, because of the danger of mobilizing the lead which may have been deposited in the bones, thus intensifying the symptoms. Since the metal is relatively inert when deposited in the bones, this should be encouraged by means of the administration of lime salts and alkaline phosphates, and perhaps adding vitamin D (viosterol, etc.) to the diet. Eventually, there is then the prospect of its gradual elimination through natural channels.

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transmission. This type of encephalitis is distinctly a winter disease, and despite its name, no extensive or sharply circumscribed epidemics have ever occurred. No age is exempt, but multiple cases in a family are rare. The incubation period is probably between one and two weeks.

The characteristic pathological lesions are those of the central nervous system, the lesions being confined almost entirely to the gray matter, especially the basal ganglia and adjacent structures. Hence, lesions may be found in the cranial nerve nuclei, the globus pallidus, subthalamic nuclei, substantia nigra, medulla and pons. In acute cases the microscope reveals marked capillary engorgement, petechial hemorrhages, small thrombi, and infiltration of cells about the vessels, with a certain amount of degeneration in the nerve cells. In chronic cases, the perivascular infiltration is less pronounced, but there is visible a greater amount of nerve cell degeneration with neuronophagia and proliferation of neuroglial cells.

*Symptoms.*—The symptoms are so varied and bizarre, and exhibit so much diversification in different epidemics as to make concise description almost impossible. The onset, in most cases, is very gradual, although occasionally the exact opposite may occur, with symptoms so stormy as to be highly suggestive of meningitis. In the latter instances there may be more or less fever, headache, vertigo, ophthalmoplegias (especially ptosis) and even some degree of neck rigidity with positive Kernig and Brudzinski and possibly convulsions. Occasionally there is violent delirium or marked choreiform movements. Within a few days, however, increasing somnolence develops and from this point the course is apt to resemble that of the common type of the disease in which the onset is more gradual. In these, so insidious is the onset as to make the exact date of its occurrence quite uncertain. Often there is a history of malaise, lassitude, and perhaps chilly sensations, occasionally with transient blurred vision or vertigo. Among the commonest early symptoms are ptosis and double vision (from strabismus), with a suggestion of masklike

facies, to be followed within a short time by a gradually increasing drowsiness. In some instances, however, instead of somnolence there is sleeplessness and hyperexcitation, superseded later by the characteristic lethargy. Although slight fever is frequent in the early phases of the disease, it has no distinctive pattern and is often overlooked. Occasionally there may be abrupt elevations to  $104^{\circ}$  F. or more for a short time, or even a typhoid course. Mild leukocytosis is the rule in the early part of the course, but the blood picture may be quite normal.

The *spinal fluid* in the acute stage of epidemic encephalitis will show, as a rule, a moderate increase in pressure and globulin, with a slight increase in cells, ordinarily less than 100, though higher counts are occasionally encountered. The cells are usually of the mononuclear variety. There is no reduction in sugar or chlorides.

As the disease progresses, the widest variation in symptoms may occur, many of them so bizarre as to make classification practically impossible. Mention has been made of the frequency with which ophthalmoplegias and somnolence occur, but it must be remembered that at times both these symptoms may be absent during the entire course. Ocular manifestations are especially infrequent in the so-called "meningitic type" in which the signs of meningeal irritation may be pronounced in the early phases, but the course is much shorter than the average, and recovery often seems complete. But of especial significance in differentiating the so-called "lethargic" encephalitis from practically all others is the great tendency for *new symptoms to appear months or even years after the onset* of the disease, indicating continued activity of the pathologic process in the brain. So we may have more or less complete coma for many months, or apparent consciousness but indifference to surroundings, changes in the psyche, tearing up bed clothes, grinding objects in the teeth, tremors in one or more extremities or twitching and perhaps rhythmical clonic movements. When the latter involve the respiratory muscles, hiccup and queer barking or clucking sounds, or

merely attacks of rapid and irregular breathing may develop. Speech is apt to be slow and drawling, and there may be spastic paralysis of one or more extremities, or transient facial weakness.

One of the most striking of these late manifestations is that referred to as parkinsonism, in which the masklike immobility of the features with staring eyes and drooling saliva, the rigidity of the muscles with slowing up of volitional movements, and the monotonous, jerky voice all suggest a marked degree of mental impairment. Tremors, too, are common, especially of the head and extremities, and the typical shuffling, hurrying gait of parkinsonism (propulsion or retropulsion) may occur. Examination of the pupils may reveal them to be normal, unequal, contracted or dilated, but more significant is the frequent failure to react to accommodation, and less commonly to light. The fundus is usually normal. Mention should also be made of the so-called "oculogyric" crises, in which there is a transient spasmodic conjugate upward deviation of the eyes. The multiplicity of symptoms is not hard to understand when one remembers the widespread distribution of the pathologic lesions, and that the process seems to be progressive, and for the same reasons it is obvious that there may be a great variety of mental symptoms indicative of changes in the higher cerebral centers, including the occasional occurrence of focal or generalized epileptic manifestations.

*Prognosis.*—This is always serious, not only because of the relatively high mortality, but also because of the many patients left with tragic sequelae which are often permanent. Although the immediate mortality varies in different epidemics, it is usually stated as between 25 and 40 per cent. It must be remembered, too, that even though the patient appears to have made a complete recovery, the disease may again flare up months or even several years later, and death possibly result. In the chronic cases, death may be the result of some intercurrent infection brought on by the long period of invalidism. Nevertheless, some patients recover completely.

—about 14 per cent, according to von Economo. The meningitic type, with rather stormy onset and short course, offers the best prognosis in this respect. Possibly if more of the milder cases were diagnosed, the outlook would appear considerably more hopeful.

*Treatment.*—This is largely symptomatic, since no specific remedy is available at present. The use of so-called "convalescent" serum is hardly justifiable because not only is it unlikely that this would influence a virus disease which has already affected the cells in the nervous system, but it is difficult to determine when a prospective donor is definitely recovered and no longer harbors the infectious agent. In the acute stage the intravenous injection of 20 per cent dextrose solution, or perhaps better, a 40 per cent sucrose (cane sugar) solution, in the same dose, occasionally seems beneficial, and supplies fluids and nourishment. Sedatives, such as phenobarbital, may be required for periods of excitement, in conjunction with hydrotherapy. In the late stages, muscular rigidity, myoclonic and ocular spasms have been treated with hyoscine hydrochloride or tincture of stramonium with occasional apparent improvement. The chief reliance, however, for all stages of the disease would seem to rest on hygienic care and keeping up the nutrition, if necessary by forced feeding through a nasal catheter.

(b) **Japanese "Type B."**—In Japan, a number of summer epidemics of encephalitis have been reported, characterized by a short, stormy course, absence of ocular manifestations, high mortality (from 50 to 90 per cent) and relatively few sequelae in the recovered cases. The disease showed a marked predilection for the older age group, although children were also affected.

*Pathology.*—The chief lesions were in the gray matter of the brain stem, cerebral hemispheres and upper levels of the cord. They consisted of hyperemia, petechial hemorrhages, perivascular infiltration of cells, with a certain amount of degeneration of nerve cells.

*Symptoms.*—The onset was frequently abrupt with high

fever and meningeal symptoms, occasionally preceded by a short period of malaise, lassitude, chilly sensations and muscular pains. Neck rigidity, positive Kernig sign and a variety of inconstant reflex changes were common, but ocular symptoms were strikingly infrequent. Fever, up to  $104^{\circ}$  to  $105^{\circ}$  F., was usually highest at the onset, and fell rapidly to normal, in most cases, within a week or ten days. Somnolence, mental confusion and tremors were common, but actual paralysis relatively rare. The spinal fluid revealed a moderate increase of mononuclear cells and globulin. In nonfatal cases, the course was short, fever three to fourteen days, and then followed rapid recovery with only occasional residual manifestations.

(c) **Australian X Disease.**—In 1917 and 1918 several small epidemics of encephalitis were reported from Australia, also in the hot season, and very similar in symptomatology to the Japanese Type B disease. Nearly 50 per cent of the cases occurred in children under five years of age, and the mortality was 70 per cent. The pathology and the symptoms were similar to those of the Japanese epidemics, and in addition, frequent mention was made of blinking of the eyes, grinding the teeth, and alternate protrusion and retraction of the tongue. High temperatures were frequent in the early phases of the disease, but ocular manifestations and involvement of the cranial nuclei were rare. The same rapid recovery and absence of residuals was noted in nonfatal cases. Cleland and Campbell reported the successful transmission of the disease to several monkeys and sheep.

(d) **The St. Louis Encephalitis Epidemic of 1933.**—This epidemic, unique in this country because of its occurrence during the summer months, and the number of persons affected within a limited geographical area, was strikingly similar in symptomatology to the Japanese Type B encephalitis. The first cases appeared in the middle of July and the disease rapidly reached epidemic proportions, eventually spreading, but to a lesser degree, to communities several hundred miles away. By the end of the epidemic, in November, it

St. Louis and the territory immediately adjacent, about 1100 cases had been reported, with a mortality of 20 per cent. Although all ages were affected, there was a distinct preference for older individuals, in whom the death rate increased with the age. There were 131 cases reported under fifteen years of age, the mortality, however, being approximately 5 per cent in this group. Multiple cases in the same household and contact between affected individuals were both very uncommon, and the method of spread is still obscure. Transmission through mosquitoes, milk and water seem fairly well ruled out.

*Etiology.*—One month after the first clinical recognition of the disease, Muckenfuss, Armstrong and McCordock announced its successful transmission to monkeys, the etiologic agent apparently belonging to the filtrable virus group. Almost immediately Webster and Fite reported equal success in infecting mice with a similar technic (intracerebral inoculation). Later it was shown that mice could also be inoculated by intranasal instillation of the virus. Serological studies on recovered patients were reported showing that a large percentage had virus-neutralizing substances in the blood, but that blood from patients who had been affected with the lethargic and other forms of encephalitis had no such properties. Tentatively, then, it may be assumed that the disease was caused by a hitherto undescribed filtrable virus.

The *incubation period* in monkeys was usually eight to fourteen days, and five days in mice. In human beings it is probably between eight and fourteen days also, although this point is still not definitely established.

*Pathology.*—The characteristic lesions are in the central nervous system and consist of intense congestion with petechial hemorrhages, cellular infiltration and degenerative changes in the nerve cells. In addition to the cuff-like infiltration of round cells about the blood vessels small focal collections of cells occurred elsewhere in the cortex, midbrain, medulla and pons and upper levels of the cord, but except in the most severe cases, there was no especial predilection for the process to involve the basal nuclei.



*Symptoms.*—The symptoms are in part those commonly observed in many systemic infections and in addition certain manifestations indicating an involvement of the central nervous system. The latter form the picture recognized as encephalitis and bear a marked resemblance to those described in the Japanese epidemics as the "Type B" infection, to differentiate it from the well-known von Economo or lethargic encephalitis. Briefly, these consisted of an abrupt onset with high fever, meningeal symptoms but without ophthalmoplegias, and in nonfatal cases, rapid recovery, as a rule without sequelae. Their more detailed description may conveniently be divided into three groups, although often one type merged insensibly into the other.

*Type I.*—The most frequent type of the disease in the 1933 epidemic was that in which the cerebral symptoms were predominant even in the early phases. Malaise and chilly sensations were complained of, together with intense headache, fever up to  $103^{\circ}$  to  $105^{\circ}$  F., and occasionally convulsions. Neck rigidity was frequent but not invariably present, nor was it an indication of the severity of the infection. At the same time, there was, in all but the mildest cases, a striking change in the mental condition, varying from mental confusion and drowsiness to marked lethargy, delirium or even coma. As a rule, however, patients could be aroused to answer questions, but were disoriented as to time and place and often had no realization of where they were, or what had transpired in the early part of their illness. Rarely, insomnia and hyperexcitation occurred instead of lethargy. Tremors, especially of the hands, tongue and lips, were common, and speech was thick and slurred and often unintelligible. In a few instances complete aphasia developed. Ataxia of a cerebellar nature was also encountered, but was rare, and usually of short duration (ten days to two weeks). The neurological signs varied in different patients and were very changeable even in the same patient. They included stiffness of the neck or spine, positive Kernig, abnormal plantar reflexes, absent abdominal reflexes (especially in adults), and irregular changes in the

knee jerks which were normal or exaggerated at certain times and perhaps absent at others. Ocular manifestations, however, such as ptosis and double vision, which are common in von Economo's type of encephalitis, were conspicuously absent in all but the rarest cases, and were then quite transient. A few patients complained of slightly blurred vision for a day or two at the onset of the disease, and occasionally slight nystagmus was noted. Pupillary reflexes and changes in accommodation were rare. The fundus was usually quite normal.

Among other but infrequent manifestations, one of the most important was paralysis, consisting, in severe cases, of mild or occasionally persistent facial weakness, and in others of spasticity of one or more extremities. Fortunately, recovery from the latter had usually occurred within one or two weeks. Mild exophthalmos was observed in some patients, but in one instance, at least, it was extreme. Changes in the pulse rate also occurred, some patients having a tachycardia, but more frequently a bradycardia was noted. The fever, which was highest in the first few days of the disease, usually fell by rapid lysis or even crisis to the normal within eight to ten days of the onset, with exceptional instances in which it persisted, of an irregular type, for several months. Likewise, mental confusion, which ordinarily had cleared up within a week or two, in severe cases remained for weeks or months after the temperature had returned to normal. As a rule, however, recovery was surprisingly rapid, and within three weeks from onset the patient was apparently entirely recovered.

The *spinal fluid*, during the acute stages, was moderately increased in amount and pressure, with a cell count, predominantly mononuclears, of from 50 to 300, or occasionally as high as 500 to 1000. The globulin was somewhat increased, but not excessively so, even in cases with a high cell count, and the sugar content was normal or slightly above this figure.

*Type II.*—In this group the encephalitis symptoms were preceded by a definite *period of invasion*, usually of one to

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*Type II.*—In this group the encephalitis symptoms were preceded by a definite *period of invasion*, usually of one to

four days' duration, but occasionally a week or more. During this time there was moderate fever, with malaise, headache, chilliness or even well-defined chills, nausea, abdominal pains, and almost invariably grippe-like pains in the back and extremities. Photophobia and mild conjunctivitis were noted in some patients, as well as mild sore throat. At this stage the similarity to influenza was marked, as the temperature, as a rule, fell within one or two days and all the symptoms were markedly ameliorated. Suddenly, however, the fever again rose abruptly, the headache became much worse, and drowsiness, mental confusion, tremors and nuchal rigidity developed. Thereafter, the course was similar to the Type I infection, the period of invasion apparently not affecting the prognosis.

*Type III.*—In this class are placed the mild or abortive cases, in which the diagnosis would probably never have been suspected but for the fact that there was an epidemic of encephalitis in the community. Some degree of fever and headache was usually present, and often a slight tremor of hands and tongue, with absent abdominal reflexes, especially in adults, these being usually normal in children, and perhaps a suggestion of neck rigidity or positive Kernig. Chilliness and muscular pains were common but milder, and the sensorium was usually clear. The spinal fluid, however, showed the same changes as those observed in the other types of infection. Recovery was, of course, more rapid in such cases, and sequelae almost never occurred.

The *blood count*, in all types of the disease, was quite variable, showing a slight leukocytosis in some cases, whereas others had a marked leukopenia. The Schilling hemogram, as a rule, showed a slight shift to the left.

*Complications.*—Most of the complications occurred in older individuals in connection with such preexisting pathology as cardiorenal disease, arteriosclerosis, hypertension, etc. The most frequent immediate cause of death, however, aside from the toxemia of the infection, was broncho- or lobar pneumonia.

*Prognosis.*—The mortality for all reported cases was 20 per cent, being higher in the aged and lowest in children (only

5 per cent in those under fifteen years of age). In nonfatal cases recovery was usually rapid and apparently complete, except for occasional subjective symptoms, such as nervousness, fatigue, apprehensiveness for the future, etc. However, in certain instances mental changes, spastic paralysis, tremors and even fever, persisted for a number of months after the initial attack. A check-up of a large number of patients one and two years after their illness failed to reveal the development of new symptoms such as is commonly observed in the old von Economo type of encephalitis. Moreover, the blood of such recovered patients in many instances showed neutralizing substances against the virus believed to be the specific cause of the infection, and hence it seems unlikely that there will be any further progression of the pathologic process.

*Differential Diagnosis.*—The grippe-like pains and aches, with chilly sensations were often mistaken for influenza or malaria in the cases with a definite period of invasion. Likewise, the leukopenia and bradycardia of others suggested the possibility of typhoid. Development of the neurologic symptoms and spinal fluid changes easily differentiated between these various infections. Tuberculous meningitis and poliomyelitis, however, provided greater problems in diagnosis. The more gradual onset of tuberculous meningitis, the tuberculous focus elsewhere, and the lower spinal fluid sugar, presence of tubercle bacilli and invariably fatal outcome usually served to distinguish between the two diseases. In poliomyelitis, the clear sensorium, absence of speech involvement and flaccid paralysis of certain muscle groups are so characteristic as to establish the diagnosis eventually. Acute disseminated encephalomyelitis associated with infections ("postinfection encephalitis") may be almost indistinguishable from the St. Louis type, particularly in nonfatal cases. In such cases, the history, and possibly tests to determine the presence in the blood stream of neutralizing substances for the specific virus of the St. Louis cases were helpful, but it must be confessed that differentiation between the two diseases was not always possible, except at autopsy.

*Treatment.*—The therapy employed was largely symptomatic. The use of convalescent serum or other so-called "specific" measures could hardly be expected to be effective, firstly, because when once a virus disease becomes established and produces symptoms, it is generally considered to be beyond the reach of specific therapy, and secondly, because in most cases recovery was so rapid as not to require any treatment beyond the general measures used in any serious infection. Dehydration of the tissues should be prevented by means of the subcutaneous injection of Hartmann's or Ringer's solution and the intravenous administration of 20 per cent dextrose or 40 per cent sucrose (cane sugar) solution. The sucrose solution is used in the same dosage as 20 per cent dextrose; both provide fluid and food, and theoretically, at least, may be of some value in lessening cerebral edema and possibly minimizing nerve cell damage. In unconscious patients and those unable to swallow, feeding may be carried out through a nasal catheter. Lumbar puncture as a rule relieves the headache, and may quiet nervous irritability, although marked delirium with hyperexcitation will perhaps require sedatives, such as phenobarbital or bromides.

#### ACUTE DISSEMINATED ENCEPHALOMYELITIS ASSOCIATED WITH INFECTIONS

(Postinfection Encephalitis, Para-infection Encephalitis, Postvaccinal Encephalitis)

It has long been known that serious disturbances of the nervous system occasionally accompany or follow one of the infectious diseases. This is especially true of those diseases caused by filtrable viruses, although clinically similar manifestations may at times follow other bacterial diseases apparently not associated with viruses. From the number of reports in the literature, it would seem that the incidence of encephalitis or encephalomyelitis of this nature has shown a considerable increase within the last few years. Since the precise factors which bring about such disturbances in the nervous system are unknown, and autopsies have been too few

to permit of their final classification on the basis of the pathological processes involved, it is convenient, for purposes of discussion, to place them tentatively in the same group.

**Etiology.**—Although postinfection encephalitis seems commonest in association with the virus diseases, there are apparently exceptions to the rule. For example, the list includes measles, mumps, pertussis, vaccination against smallpox (vaccinia) and less frequently, rubella, varicella, variola, antirabic inoculations, scarlet fever, typhoid and paratyphoid fever, lobar pneumonia and bacillary dysentery. In addition to these, a number of cases of encephalitis have been reported associated with influenza or upper respiratory symptoms, although it is not clear whether such participation of the respiratory tract represents the early manifestations of the encephalitic period of invasion, or constitutes the predisposing cause.

Because of the similarity of the encephalitic symptoms in otherwise widely different diseases, it has been suggested that the encephalomyelitis is a separate and distinct disease, due to some hypothetical, specific neurotropic virus which in some way becomes activated by the antecedent infection. However, this question cannot be definitely answered in the present state of our knowledge.

**Pathology.**—Although the small number of careful autopsy studies does not permit of definite conclusions in the case of each one of the diseases mentioned, the pathologic picture has been well established as quite similar in the encephalitis of measles, smallpox vaccination and antirabic inoculations. The same is apparently true of variola, varicella, rubella, and possibly some of the other diseases, although the reports are too few to establish this with certainty. The characteristic lesions of the central nervous system are areas of perivascular demyelination and a cuff-like ring of mononuclear cells about the blood vessels. Petechial hemorrhages and congestion are common, but as a rule, there is relatively little injury to nerve cells or axis-cylinders. The process affects both gray and white matter, the lesions in the latter



being usually more extensive. Not infrequently they involve the cord as well as brain.

The pathology of pertussis encephalitis reveals less tendency to destruction of nerve cells, with areas of cerebral atrophy as a late result. It is quite possible, too, that in mumps encephalitis and "mumps meningitis" the lesions differ from those in measles, for example, but autopsies are so infrequent in mumps as to leave this point unsettled. Indeed, it is not known whether mumps meningitis and encephalitis are really the same disease, possibly a meningo-encephalitis, differing only in the degree and location of the lesions, or two entirely different processes.

**Symptomatology.**—*Measles.*—Encephalitis is commoner after measles than any other of the exanthemata. The onset is usually two to five days after the first appearance of the rash, rarely in the prodromal period, and the occurrence of neurologic symptoms apparently bears no relation to the severity of the infection up to this time. Its appearance is sudden, with headache, vomiting, possibly a brief exacerbation of the fever, and almost at once there appear drowsiness, often convulsions, and not infrequently a slightly stiff neck and positive Kernig. Paralysis, either flaccid or spastic, of one or more extremities may occur, and twitching of the muscles, coarse tremors, irritability and aphasia. At times there is delirium or mental confusion. Convulsions are especially common in children, and apt to be repeated during the early part of the illness. Changes in the tendon reflexes and abnormalities of the plantar reflexes may be present, but except in the severer cases, this does not persist for more than a few days.

Other manifestations which may be observed include difficulty in swallowing, facial weakness or paralysis, usually transient, and ataxia of a cerebellar type. Ptosis and double vision are rarely observed. When the process involves the spinal cord, there are usually disturbances of sensation and in the function of the bladder and rectum, and at times a flaccid paralysis of the lower extremities which is often as complete as in any other form of transverse myelitis. Indeed, in general

cord lesions are slow in clearing up and unfortunately may result in permanent disability.

*Prognosis.*—The subsequent course of the encephalomyelitis is variable, but in probably the majority of cases, recovery is rapid and complete. It is almost incredible that a child with convulsions, aphasia or coma and perhaps complete paralysis of all extremities may seem fully recovered within three or four days after the onset of this illness. In other cases, however, spastic paralysis, tremors and mental deterioration may persist for months, or even be permanent. Cord lesions are somewhat more apt to be followed by such residuals than are the cerebral ones. The mortality rate is probably around 10 per cent, death resulting within a week or ten days as a direct result of cerebral damage, or it may occur much later from emaciation, exhaustion, or some intercurrent infection.

*Treatment.*—Lumbar puncture may relieve headache and irritability, and intravenous injections of 40 per cent sucrose (cane sugar) or 20 per cent dextrose solutions tend to relieve the cerebral edema and possibly lessen nerve cell damage. The latter measures also supply nutrition and fluids to the body. Subcutaneous administration of Hartmann's or Ringer's solution is of value at times. Otherwise the treatment is symptomatic, the use of convalescent measles serum being both illogical and ineffective.

*Rubella.*—The encephalitic symptoms appear as a rule one or two days after the first appearance of the rash. Although less common than in measles, the symptoms are in every way comparable. The pathology is assumed to be similar also, although there is insufficient evidence on which to base a positive statement in this respect.

*Variola and Varicella.*—The encephalomyelitis which occasionally occurs is apparently similar to that of measles, the symptoms usually appearing two or three days after the rash comes out, but occasionally they may be as late as the seventh to tenth day.

*Vaccination Against Smallpox.*—During the past decade

an ever-increasing number of cases of postvaccinal encephalitis and myelitis have been reported from practically all over the world, being apparently most numerous in Holland. At that, however, the incidence is only 1 in several thousand cases. It is less common in infancy, and although it may occur even after secondary or revaccination, it is considerably more frequent after primary inoculations. There is considerable evidence to show that the causative agent is not contained in the vaccine virus itself, since even when the same vaccine is used, the incidence of encephalitis is much greater in regions where post-measles encephalitis is known to be prevalent than in countries where it has been less common. The pathology, however, is quite similar to that in measles, affecting the gray and white matter of brain and cord, and the characteristic lesion being a process of perivascular demyelination.

The *symptoms* are similar to those occurring in measles, appearing usually ten to twelve days after vaccination, but occasionally earlier or as late as three or four weeks after vaccination. Fever of brief duration, headache, vomiting and drowsiness or coma appear, often accompanied by slight neck rigidity, positive Kernig and changes in the plantar and tendon reflexes. Convulsions are common, and may be followed by spastic paralysis of one or more extremities. Flaccid paralysis of the legs, associated with incontinence of urine and feces, indicates spinal cord involvement. Speech may be affected, up to the point of complete aphasia, and tremors of hands and lips may be noted. A less frequent occurrence, fortunately not apt to be permanent, is mental deterioration to the point of apparent idiocy. The spinal fluid shows a moderate increase in globulin and mononuclear cells.

*Prognosis.*—The mortality is usually stated as about 50 per cent, although in our own series of cases it was about the same as in measles, around 10 per cent. In nonfatal cases, recovery is often complete and surprisingly rapid, so that the child may appear to be normal within less than a week of onset. Residual manifestations occur at times, and especially in those with spinal cord lesions.

*Prophylaxis.*—Whenever possible, vaccination against smallpox should be carried out in infancy, since the incidence of encephalitis at this age is decidedly lower than in later life. However, it may be wise to defer vaccination at such times as infections of the central nervous system (*c. g.*, poliomyelitis, epidemic encephalitis) are prevalent in the community. Moreover, Armstrong has suggested that children be immunized against diphtheria before being vaccinated against smallpox, since diphtheria toxoid apparently renders mice more resistant to intracerebral inoculations with vaccine virus. Again, Rivers has advised using intradermal inoculations of culture virus instead of the usual calf lymph, since he feels the purity of the product and the mildness of the reactions produced may avoid the sequel of encephalitis.

*Treatment.*—This is similar to that described under measles encephalitis. It has been suggested that the serum (usually 10 cc. or more) from another individual who gives a history of a recent successful vaccination be used intravenously or intramuscularly, but it seems unlikely that this would ever prove effective, once the disease is established and symptoms have appeared.

*Antirabic Inoculations.*—During the Pasteur treatment for the prevention of rabies in rare instances the development of encephalitis has been reported. Pathologically and clinically this appears to be similar to that associated with vaccination against smallpox and in measles. The same process of demyelination occurs, and the course and prognosis are similar to those described above. The symptoms may appear at any time during the course of the treatment, but especially during the last of the series of injections.

*Mumps.*—Symptoms referable to the central nervous system occasionally occur in mumps, and in the absence of data concerning the pathological process, are usually divided into two clinical groups, mumps encephalitis and meningitis. It is possible that the two are really variations of the same disease, a meningo-encephalitis. In mumps meningitis, the onset is usually at the height of the disease, or may even precede the

involvement of the salivary glands; there is high fever, and invariably stiff neck and positive Kernig and Brudzinski signs. The spinal fluid shows a high cell count (5000–6000 or more), the mononuclear cells predominating. In the encephalitic form, on the other hand, the meningeal signs are less prominent and the cell count lower, as in measles and postvaccinal encephalitis. Despite the serious symptoms, recovery, even in meningitis, is the rule, although in rare instances the patient may be left with a permanent spastic paralysis of one or more limbs, blindness, deafness, or even idiocy.

*Pertussis.*—The neurological complications of whooping cough are well known and relatively common. This is especially true of convulsions without other evidence of cerebral injury. But occasionally there is a sudden onset of paralytic symptoms, often a hemiplegia, with somnolence or even coma. Inasmuch as nosebleed and subconjunctival hemorrhages are quite frequent in pertussis as the result of the severe paroxysmal cough and its changes in the circulation, the paralysis may be attributed to intracranial hemorrhage and perhaps operation advised. However, encephalitis should always be ruled out first, and a search made for stiff neck, and positive Kernig, which, in the absence of fundus or blood pressure changes, would speak more for encephalitis than hemorrhage. In encephalitis the spinal fluid shows the characteristic increase of mononuclear cells, but lumbar or cistern puncture should be performed most cautiously after careful examination of the patient, for in hemorrhage the brain may be jammed down into the foramen magnum and sudden death result from spinal drainage. In encephalitis the coma and paralysis often clear up within a few days, but occasionally residuals, such as spastic paralysis, tremors, visual disturbances or mental changes may persist for weeks, or even be permanent.

It seems likely that the pathological changes in pertussis encephalitis are somewhat different than the others described above, although the question cannot be settled until more autopsy studies are available. Reports have mentioned a more

extensive atrophy of the cortex and neuron degeneration, without reference to myelin destruction. Including this type of encephalitis in the postinfection group, however, seems justifiable on the basis of clinical symptoms until further knowledge of the condition is gained.

*"Influenza" and Other Respiratory Infections.*—In many cases of encephalitis which, except for the antecedent infection, are indistinguishable from the postinfection type described, there is a history of a preceding group of mild upper respiratory or influenza-like symptoms. These include mild sore throat, rhinitis, chilly sensations, headache, lassitude, prostration, and pains in back, limbs or abdomen. It is impossible to say at present whether these constitute the predisposing cause, or represent the invasive symptoms of the encephalitis itself. But, in some instances, the encephalitis has followed a definite lobar or bronchopneumonia. The neurologic manifestations are similar in onset and course to those seen in measles, after vaccination, etc. The prognosis is apparently about the same, many cases showing a surprisingly rapid recovery, and residuals being only occasionally met with.

*Encephalitis Associated with Other Infections.*—Encephalitic symptoms similar in every way to those after measles are occasionally seen in association with other infections. In our experience, this occurs oftenest after typhoid fever, during the period of convalescence, but it has also been observed after paratyphoid, scarlet fever, bacillary dysentery and even pyelitis. They may be placed in the postinfection group of encephalitides until further knowledge permits of a more accurate classification.

#### UNCLASSIFIED TYPES OF ENCEPHALITIS

Numerous reports have appeared in the literature describing an encephalitic syndrome under various names, among which may be mentioned "serous meningitis," "acute benign idiopathic serous meningitis," "acute aseptic meningitis," "acute lymphatic meningitis," "meningismus," etc. In most instances the symptoms consist of signs of meningeal irrita-

tion, with an increase of pressure, globulin, and mononuclear cells in the spinal fluid. With the exception of a group of cases in young children described by Brown and Symmers, most of these cases cleared up rapidly, the patients showing no residual manifestations.

Under the name of "acute serous meningitis" Brown and Symmers described a group of 10 cases, all terminating fatally, in which the symptoms began abruptly with irritability, vomiting and diarrhea, frequently a sore throat, and high fever. Among other symptoms they mention convulsions, coma, irregular respiration, ptosis and strabismus, nystagmus, papilledema, muscular twitchings, retraction of the angles of the mouth, neck rigidity with positive Kernig and occasionally paralysis. Pathological studies showed a marked hyperemia and edema, and at times vacuolization of the ground substance and cloudy swelling of the pyramidal cells. There seems no way at present of arriving at a more accurate classification of this type of case. Indeed, it is highly important that experiences with various types of encephalitis, and especially those fatal cases in which careful autopsies have been performed, be placed on record to further a better understanding of the subject.

## CLINIC OF DR. H. L. ALEXANDER

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### THE EARLY DIAGNOSIS AND TREATMENT OF EMPHYSEMA

UNTIL a few years ago, a good deal of confusion existed concerning the significance of emphysema. Given two barrel-chested individuals with evident emphysema of approximately the same degree, one may be completely disabled because of dyspnea on slight exertion and the other capable of hard physical labor. The separation of patients into two groups, those with symptoms of respiratory dysfunction, notably dyspnea and cyanosis, and those without such symptoms, has led to clarification.<sup>1</sup> The latter patients, in whom their apparent emphysema seems no handicap, were found to have a stiffness of the spine. Investigation of this lesion revealed that all such cases were due to a swelling of the intervertebral disks which resulted in a straightening of the spine. Since the ribs are attached posteriorly to the vertebrae, then, as the back straightens the ribs elevate. The same effect is observed when an individual stands up very straight. His ribs are thrown upward, and a typical barreling of the chest results (Figs. 27, 28). The lungs follow the chest wall as the process develops, but there is nothing inherently wrong with them. Patients with so-called "senile emphysema," so commonly seen, have stiffened spines in which degenerative processes in the disks are present. As the lesion progresses the bony substance of the vertebrae becomes involved, and finally the spine may collapse (Fig. 29), and dorsal kyphosis occurs. The barrel



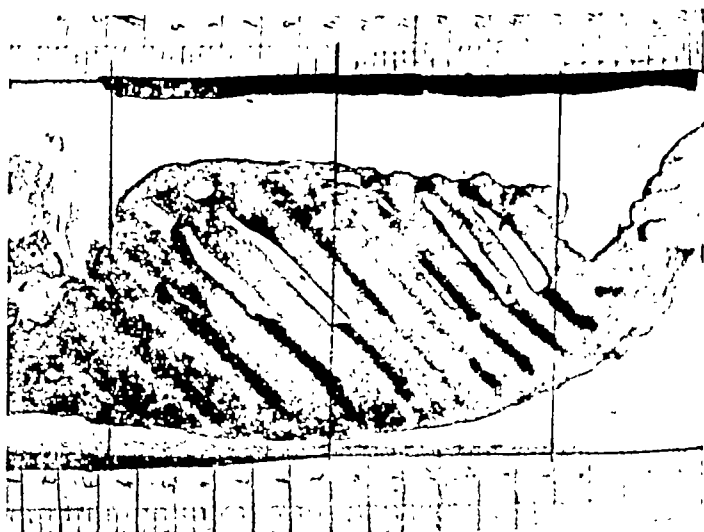


Fig. 27.—Thoracic cage of a normal cadaver from which all muscle has been removed. The upper edge of the sternum stands at 15 inches on the scale. (From Kountz and Alexander in "Medicine," September, 1934, Williams and Wilkins Co., Publishers.)

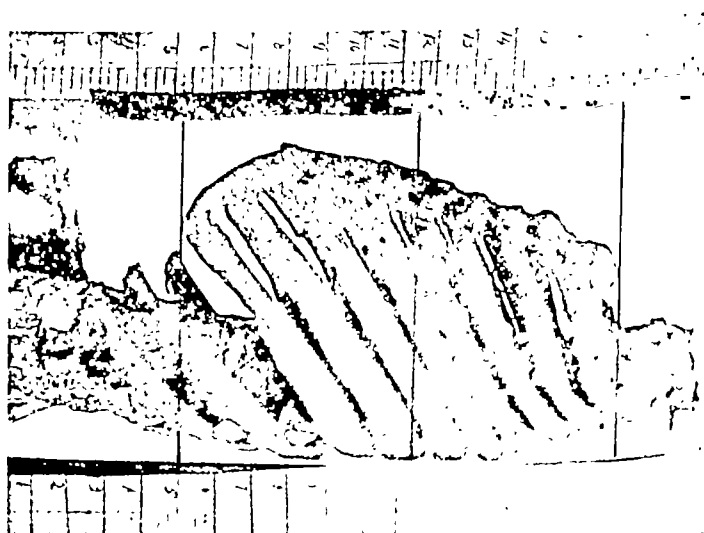


Fig. 28.—The same model as Fig. 27. The thoracic spine has been straightened. The upper edge of the sternum stands at 17 inches. The distance of the chest from the spine to the sternum has been increased  $1\frac{1}{2}$  inches. (From Kountz and Alexander in "Medicine," September, 1934, Williams and Wilkins Co., Publishers.)

chest then becomes exaggerated, but the lungs, other than stretching moderately to keep in contact with the changing chest wall, do not suffer structural damage. Vital capacity and oxygen saturation values in the arterial blood usually remain within normal limits unless there is a coincident cardiac failure.

The first step in the diagnosis of emphysema is to distinguish whether the barreling of the chest and hyperresonant lungs are due to a lesion of the lungs or of the chest wall. If



Fig 29.—Spine cut longitudinally from a case of postural emphysema. The swollen intervertebral disks with invasion of vertebral bodies and collapse of the spine are seen.

the latter, it is of little consequence, since this is not really emphysema in a pathological sense, as the lungs are neither structurally nor functionally involved. Such cases are easily distinguished from those with true emphysema. Measurements of vital capacity are within normal limits, there is no cyanosis, no dyspnea, and the diaphragm has free movement. Moreover, the dorsal spine is limited in its movement, and the thoracic curve is either flattened out or in the late cases with collapse, greatly exaggerated. These patients with so-called

"postural emphysema" represent the majority of cases and require only diagnostic consideration.

TABLE 1  
*Postural emphysema*

PATIENT NUMBER	VITAL CAPACITY	PER CENT* OF NORMAL VITAL CAPACITY	ARTERIAL BLOOD PRESSURE	VENOUS PRESSURE	OXYGEN CONTENT ARTERIAL BLOOD	PER CENT OF SATURATION OF ARTERIAL BLOOD WITH O <sub>2</sub>
	cc.			cm. water	vols. per cent	
1	3,200	89.9	160/90	5	18	96
2	3,400	90.8	140/85	4.5	17.4	
3	3,800	92	168/78	4.5	17.2	95
4	3,600	85	205/98	6	18.2	94
5	3,300	87.4	165/87	8.2	17.6	93
6	2,600	75.2	175/100	5.5	18	94
7	4,000	100	140/87	4		
8	3,200	87	175/105	4		
9	3,700	90	160/90	4.4		
10	3,900	96	127/82	5.4	18	94.2
11	2,700	80	154/98	4.8		
12	2,800	85	120/80	5		
13	3,300	90	132/82	5.5	17.8	95
14	3,500	85	210/120	5		
15	3,600	84	196/105	5.5		
16	3,900	92	187/99	5.8	18	95.2
17	4,000	102	130/87	4.8	18.1	94.3

\* Based on Dreyer's Tables.

(From Kountz and Alexander in "Medicine," September, 1934, Williams and Wilkins Co., Publishers.)

True emphysema in which the alveoli are stretched and torn is a serious disease because the structural damage to the lungs is irreparable. It results from bronchial obstruction with few exceptions, such as extreme compensatory emphysema after a large portion of the lungs has been destroyed. emphysema induced by work at very high altitudes, and the great stretching and tearing of pulmonary tissue occurring occasionally during prolonged confinement in certain respirators. The forces of inspiration, which pull air past partially occluded bronchi, are greater than those of expiration which depend largely on the elasticity of the lung, and the squeeze of thoracic and abdominal muscles. In the course of time air accumulates distal to the bronchial obstruction, and the alveoli distend to the point of loss of elasticity and final rupture.

The commonest causes of bronchial obstruction are the lesions of asthma and bronchitis. The sticky exudate from overacting mucous glands tends to plug the finer airways, and the smooth muscle in the walls of the bronchi, greatly hypertrophied after years of bronchospasm and cough, remains in a state of hypertonus, so that there is more or less constant spasm. Distal to this narrowing, which occurs chiefly in the bronchioles, more and more air becomes trapped.

The acute ballooning out of the lungs during a paroxysm of bronchial asthma, wherein the position of deep inspiration is assumed, portrays in part what occurs when the lungs are chronically distended. The diaphragm is flattened out in its position of contraction, because the lungs crowd downward toward the abdominal space as they gradually enlarge. As they continue to distend the intrapleural pressure increases, and the thorax in time takes the position of deep inspiration. With the diaphragm held in the position of contraction and the chest distended, the ability to take a deep breath is greatly impaired. Measurement of vital capacity, which records the amount of air exhaled from deepest inspiration to greatest expiration, is reduced at times 75 per cent below normal values. The patient then is unable to do any exertion without shortness of breath.

Unfortunately, neither the frequency nor significance of obstructive emphysema is generally recognized. Many such patients are thought to be suffering from heart trouble, since the symptoms and signs of cardiac decompensation and true emphysema are the same. These include dyspnea, cyanosis, râles in the chest, low vital capacity and high venous pressure. Treatment of the heart brings no improvement excepting in cases in which the heart eventually becomes affected.

The diagnosis of true emphysema in its early stages becomes important, since not much can be accomplished after the lungs have been largely destroyed. Moreover, dyspnea does not occur until the disease has progressed far, so that early recognition is of great advantage. The first step is to be conscious of the fact that the great majority of patients

with chronic bronchitis and prolonged asthma sooner or later develop emphysema. The next is to place such patients under the fluoroscope and observe diaphragmatic excursions. As stated above, the early direction of pulmonary distention is downward. Normally, as the diaphragm contracts it moves toward the abdomen from its domed position of relaxation, and its vertical excursion may measure some inches on deep

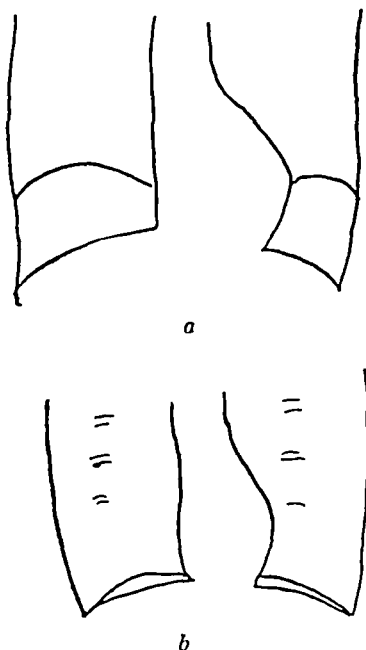


Fig. 30.—Orthodiagrams of maximum diaphragmatic excursion, *a*, in a patient with postural emphysema; *b*, in a patient with asthma and obstructive emphysema. The patient was of the same general body type in each case (From Kountz and Alexander in "Medicine," September, 1934, Williams and Wilkins Co., Publishers.)

inspiration. When encroached upon by the distending lungs and pushed down toward its position of contraction, its movement becomes less and less and finally ceases. Breathing is done then entirely with the thorax (Fig. 30).

If a patient with bronchitis or asthma shows limitation of movement of the diaphragm, his vital capacity should be taken on any ordinary spirometer. Normally this should be 3500 to

4000 cc. or more for adults. If the vital capacity remains at such values, the emphysema has not progressed to the point of interference with respiratory function. Lower readings even without symptoms of dyspnea indicate probable structural alveolar changes (Table 2).

TABLE 2

*Obstructive emphysema*

PATIENT NUMBER	VITAL CAPACITY	PER CENT* OF NORMAL VITAL CAPACITY	ARTERIAL BLOOD PRESSURE	VENOUS PRESSURE	OXYGEN CONTENT ARTERIAL BLOOD	PER CENT OF SATURATION OF ARTERIAL BLOOD WITH O <sub>2</sub>
	cc.			cm. water	vol. per cent	
1	1,300	52	110/80	16	14.2	77
2	1,700	50	105/72	8	16.7	87
3	2,400	60	112/75	12.2	17.7	
4	2,200	58	120/80	8.5	16.8	90
5	2,500	55	107/60	7.2	15.2	
6	2,200	48	130/80	12	15	86.4
7	1,800	48	105/72	9.5	14	82
8	1,700	43	115/85	10.7	16	90
9	2,600	66	160/90	9.5	16.5	85
10	2,700	72	130/85	13.5	16	90

\*Based on Dreyer's Tables.

(From Kountz and Alexander in "Medicine," September, 1934, Williams and Wilkins Co., Publishers.)

Physical signs may reveal early emphysema long before barreling of the chest has occurred. Hyperresonance of the lungs, high-pitched vesicular breathing, impairment of movement at the bases and partial obliteration of the area of cardiac dulness are typical. Roentgenograms show hyperventilated lung fields, wide separation between the anterior ribs, a low diaphragm and a spindle-shaped heart which becomes elongated as its base is pulled downward by the diaphragmatic descent.

The search for emphysema in all patients with chronic asthma and bronchitis by observations of diaphragmatic movement, of vital capacity, physical signs and roentgenograms leads to the early recognition of the disease.

Inasmuch as most cases of emphysema result from asthma and bronchitis, prophylaxis consists in adequate treatment of

these two disorders, details of which are beyond the scope of this presentation.

The therapy of emphysema is entirely symptomatic. In the advanced stages there is usually deterioration of health. Anorexia, undernourishment, broken sleep, and loss of muscle tone from inactivity require special attention.

Especial consideration should be given to the bronchial lesions with the purpose of lessening obstruction. A warm climate is desirable because cold air induces cough. If travel is not feasible, warm moist air at home may be secured by simple humidifiers or even with a steam kettle. The dry, dusty air of overheated rooms is distinctly irritating to the bronchial mucosa.

One of the principal causes of cough is the outpouring of tenacious secretion from the mucous glands in the bronchial walls. By lessening the viscosity of the sputum, cough discharges it more easily. Potassium iodide and ammonium chloride are good drugs for this purpose, and are given in 0.3 Gm. doses every two hours, preferably with a cup of water.

The bronchial muscle has been found to be hypertrophied in all cases of emphysema with the exception of a few very advanced ones. Excessive secretion and bronchospasm are the essential lesions which narrow the air ways, and epinephrine has been found to give immediate relief in most cases with marked dyspnea on slight exertion. The drug acts by stimulating the sympathetics and thereby lessens the parasympathetic stimulation of the bronchial muscle and glands. Measurements of vital capacity taken before and after administration of 0.5 cc. of adrenalin chloride<sup>2</sup> showed an increase as high as 40 per cent whereas in normals the increase is about 10 per cent. Ephedrine in doses of 0.02 Gm. given three or four times a day over a long period has been found more useful than any other single pharmacologic measure.

In cases where there is marked overdilatation of the lungs it has been found possible to raise the flattened diaphragm to its position of relaxation from which it can again contract. By so doing the normal process of breathing is resumed. As a

result, the vital capacity is increased, and dyspnea is lessened. This is accomplished by the use of an abdominal belt so devised that pressure is exerted over the lower abdomen just above the symphysis pubis.<sup>3</sup> The belt is made of canvas or leather and fits around the abdomen well below the umbilicus (Fig. 31). A pad of sponge rubber attached to the inner

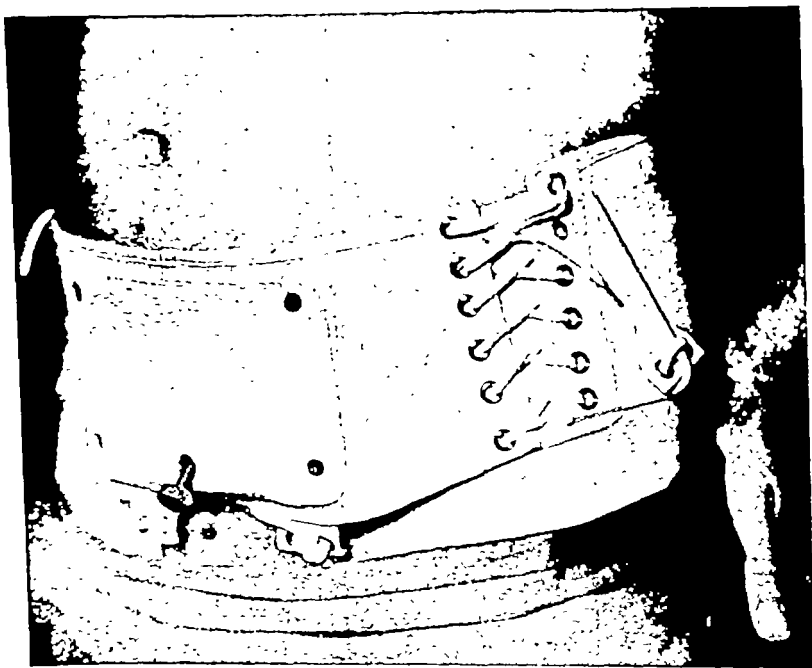


Fig. 31.—Abdominal belt in place. The pad of sponge rubber attached to the inner side of the belt exerts pressure upward and inward in the direction of the screw bolt seen protruding from the lower binder of the belt. A new locking device has supplanted the bolt.

surface of the belt anteriorly is directed inward and upward toward the promontory of the sacrum by means of a steel spring and locking device which can be adjusted from without to suit the comfort of the patient. By such an arrangement pressure is directed upward to the under surface of the diaphragm which is lifted toward the thorax. From its new position of relaxation it contracts, but since the elasticity of



the lungs is lost, they are thrust back by pressure from below during each expiratory phase. Once the belt is adjusted, it is a very effective measure in making breathing easier.

To conclude, the diagnosis of emphysema rests first with the separation of cases due to bronchial obstruction from those of the postural type. The early recognition of the disease depends on fluoroscopic observations of diaphragmatic movement, and measurement of vital capacity in all cases with chronic asthma or bronchitis which emphysema constantly follows. Physical signs reveal the underlying pulmonary distention.

Treatment is directed toward lessening bronchial obstruction and facilitating breathing by mechanically restoring the diaphragm to its normal position.

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CONSTIPATION: THE LAXATIVE VALUE OF BULKY  
FOODS

CONSTIPATION is a symptom rather than a disease. For a full discussion of its etiology one should consult Hurst.<sup>1</sup> Regardless of its numerous causes we agree with Hurst when he says, "Nearly all patients with constipation are benefited by a suitable diet, even if other treatment has to be simultaneously used." The purpose of this paper will be to discuss the physiological actions of indigestible food residue and to give some practical suggestions in the use of foods for relief of this symptom.

The initial interest of one of us (W. H. O.) began over a dozen years ago with an effort to determine how much absorbable carbohydrate was destroyed by intestinal bacteria. As a measure of the destruction of carbohydrate we took the amount of acetic acid appearing in the stool. In passing, let us say here that the weight of evidence indicates that the stool fatty acids are the best criterion of the extent of carbohydrate fermentation. This work<sup>2</sup> showed that the stool volumes of our experimental subjects were much higher on diets predominantly composed of sugars or starches than on diets in which protein or fat predominated and that simultaneously with the augmented stool volume of high carbohydrate feeding, the stool volatile fatty acids increased. Lactic acid, which in pure cultures is as frequently produced, and in as large

amounts, as the volatile fatty acids, cannot be demonstrated in the stools. Pittman and Olmsted<sup>3</sup> found that lactic acid added to fresh stool material was destroyed. We felt sure that the volatile acids produced on high carbohydrate diets were stimulating to the colon and that the increase in stool bulk was due to increased peristalsis. Since the indigestible carbohydrates are much more effective in increasing stool bulk, we wondered whether in their case also the effects on the intestine might be from the fermentation of cellulose rather than because of their mechanical distention of the intestine, the explanation which has usually been offered.

Indigestible residues consist of cellulose, lignin and hemicellulose. If one examines the analytical data of any cereal, the words cellulose, lignin and hemicellulose do not appear, but one finds the term crude fiber, referring to a method which was devised seventy years ago at Weende, Germany, and today widely accepted by agricultural chemists. According to the method any cereal or vegetable material is digested with both boiling dilute acid and alkali for a given time and the acid and alkali soluble products filtered off. What remains after this double digestion is called crude fiber. Williams and Olmsted,<sup>4</sup> in a recent paper, showed that crude fiber represents only a variable fraction of the combined cellulose, lignin and hemicellulose. The crude fiber method is of no assistance in determining the individual fate of cellulose, lignin or hemicellulose in the intestinal tract. For this reason Williams and Olmsted defined indigestible residues and proposed a biochemical method for isolating them from the stools and determining separately the amounts of cellulose, lignin and hemicellulose. The method uses simple biological technics for separating true residue from interfering substances in feces or stools and well-recognized chemical methods for subsequent analysis of the residue. The method offers several advantages among which are: (1) It separates indigestible residue into its proper fractions and quantitatively determines each fraction whether in feces or foods. (2) It has been applied to a wide variety of materials and has enabled us to account

for essentially 100 per cent of such materials. Such an analysis by older procedures has been impossible and in such a material as wheat bran 15 to 50 per cent was unaccounted for. With this method not only can the cellulose, lignin and hemicellulose be quantitatively determined in any foodstuff, but after ingestion they can be accurately estimated in the stools.

TABULATION

	Cellulose	Hemi-cellulose	Lignin
Wheat bran	Low	High	Moderately high
Alfalfa leaf	High	Low	High
Corn germ meal	Low	High	Low
Carrots	High	High	Low
Cotton seed hull	Low	High	High
Sugar beet pulp	High	High	Low
Peas	High	Low	Low
Cabbage	High	High	Low
Agar	None	High	None
Cellu flour	High	Low	None

Equipped with this improved technic we concentrated by simple bland procedures the indigestible portions of ten foodstuffs, analyzed the materials and added them to the foods of experimental subjects on a residue-free diet.<sup>5</sup> The resultant stools were weighed and analyzed by the same method. The comparative analyses of material fed with the material recovered in the stool indicated precisely how much cellulose, lignin and hemicellulose disappeared. A comparison of the weight of the stool on the nonresidue diet with the stool weight when the indigestible materials were added, showed to what extent each material affected bulk. The ten materials selected represented three types of indigestible residue: first, materials whose source was cereals; second, materials whose source was vegetables; and third, materials which had been processed in a manner chemically similar to that used in the production of crude fiber. Representatives from the first type were wheat bran, corn germ meal (this is the remainder of the corn germ after the corn oil has been pressed out) and cotton seed hull (the ground-up hulls of the cotton

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Agar	None	High	None
Cellu flour	High	Low	None

Equipped with this improved technic we concentrated by simple bland procedures the indigestible portions of ten foodstuffs, analyzed the materials and added them to the foods of experimental subjects on a residue-free diet.<sup>5</sup> The resultant stools were weighed and analyzed by the same method. The comparative analyses of material fed with the material recovered in the stool indicated precisely how much cellulose, lignin and hemicellulose disappeared. A comparison of the weight of the stool on the nonresidue diet with the stool weight when the indigestible materials were added, showed to what extent each material affected bulk. The ten materials selected represented three types of indigestible residue: first, materials whose source was cereals; second, materials whose source was vegetables; and third, materials which had been processed in a manner chemically similar to that used in the production of crude fiber. Representatives from the first type were wheat bran, corn germ meal (this is the remainder of the corn germ after the corn oil has been pressed out) and cotton seed hull (the ground-up hulls of the cotton

seed). Representatives of the second type were carrots, alfalfa leaf, peas, cabbage and beet pulp (the latter is the pulp of the sugar beet after the juice has been extracted). All these materials were coarsely ground, washed overnight with water at 60° C., air dried, and ground to pass a 20-mesh sieve (but not through a 40-mesh) and finally extracted with alcohol. A pound or two of concentrated material from the vegetables represented large amounts of raw materials because the indigestible residue of carrots, cabbage, and peas amounts to from 2 to 3 per cent of the green weight.

The analyses of these products differed in the content of cellulose, lignin and hemicellulose. Most of the materials were concentrated so that the combined cellulose, lignin and hemicellulose represented from 50 to 80 per cent of the total dry weight. The cellulose ranged from 16 to 35 per cent. The lignin in most of these materials was very small. There was enough lignin in bran (8 per cent), alfalfa leaf (15 per cent), and cotton seed hull (21 per cent) to judge the effects. Hemicelluloses ranged from 10 to 35 per cent. Agar was entirely hemicellulose, *i. e.*, 81 per cent. The individual characteristics of these materials is simply summarized in the tabulation. When such materials were fed to subjects on a constant basal, nonresidue diet, the results plainly showed that those materials which contain the most hemicellulose were most efficacious in increasing the weight of the stools. Those materials which contained cellulose were not particularly helpful unless they also contained hemicellulose. Thus cellulose, which is almost entirely cellulose, scarcely increased the weight of the stools above the basal; and peas, which were very high in cellulose but low in hemicellulose, were quite ineffectual. Lignin is not only inactive but whenever present apparently counteracts the effects of hemicellulose. Thus cotton seed hull, which contains a large amount of hemicellulose but also 20 per cent of lignin, did not increase the stool weights to any considerable degree. Alfalfa leaf, a product high in lignin, high in cellulose but low in hemicellulose, only moderately increased the stools.

When the stools were analyzed for the amount of these materials that disappeared, it was of interest to find that the loss of hemicelluloses was greatest. In most instances well over 60 per cent and in three of the materials over 80 per cent disappeared. Only where the lignin was high were bacteria unable to attack the hemicellulose. Cellulose disappeared to a less extent, but bacteria were able to attack it and usually between 50 and 60 per cent was lost. Assuming the volatile fatty acids as the best index of the fermentation of the cellulose and hemicellulose we found their excretion to be greatest when the greatest amount of cellulose and hemicellulose disappeared.

We consider the impressions of our human subjects to be one of the most valuable criteria of the laxative value of the materials. From the standpoint of the subject's sensations of a satisfactory bowel movement, it is the moist, plastic, voluminous stool that is most satisfactory. Interestingly enough it was those materials high in hemicellulose, such as agar, sugar beet pulp, cabbage, and carrots, which gave the most satisfactory stools. In this respect bran, because of its wide use, is important to consider. The stools from it are very bulky but tend to be dry and often irritating. The conclusions in this research were definite, namely (1) that lignin is to be avoided, (2) that cellulose is useful but not nearly so effective as the hemicelluloses. We believe that we are the first to emphasize the differences in the action of cellulose, lignin and hemicellulose on the bulk of the human stool.

#### INFLUENCE OF INDIGESTIBLE RESIDUE ON DEFECATION

The addition of indigestible residue to the food results in stools of greater weight than can be accounted for by water and the residue escaping degradation. It has been known since the work of Strausburger that half of the stool is composed of bacteria and the greatest part of these are dead. In addition to the bacteria there is in the stools of the fasting animal and in the stools passed on a nonresidue diet, some fat, nitrogen, and minerals arising from the succus entericus and



from the remainder of unabsorbed bile and pancreatic juices. When the diet contains considerable amounts of indigestible residue, the water content is increased, and the total daily output of all of the solids appearing in the fasting stool are increased. More nitrogen, fat and starch are lost. Much of the loss in nitrogen and starch in a diet high in vegetables or whole grain cereals is due to the fact that the intestinal digestive juices are unable to penetrate through the cell membranes and thus some of the digestible protein and starch escapes absorption. It may be that even the mixing of indigestible residue with digestible food material will result in less efficient absorption because of the hastened passage through the intestinal tract. Thus when indigestible residue is added, the increase in bulk of the feces is due not only to water and the indigestible material but to an increase in fats, starch, protein and minerals and all other normal solids which usually appear in the stool. However, the loss in calories resulting from bulky stools is not great, probably (as shown by Rubner) not over 10 per cent more than is lost when the diet is free of indigestible residue.

Hurst, and recently Garry,<sup>6</sup> discuss fully the physiological movements of the colon. When the normal bowel empties itself, there is a mass peristalsis which entirely empties the whole descending colon from the splenic flexure downward. Feces are constantly present in the cecum, ascending and transverse colon. This fact explains the reason why so often materials do not appear in the feces for many days after their ingestion. Following a normal defecation feces collect in the descending colon down to the rectosigmoidal junction. Normally there are no feces in the rectum. The call to stool is due to the passage of feces from the sigmoid colon into the rectum. Anyone who does routine digital rectal examinations must be impressed with the frequency of inspissated feces particularly in the rectums of women. The call to stool sensation is lost in such individuals, but when the feces descending into the rectum are bulky, the call to defecate is more insistent.

The absorption of water that has taken place in the cecum and transverse colon leaves the feces in a semisolid state in the descending colon. If absorption of water in this part of the colon results in the loss of the plasticity of the mass, the evacuation by mass peristalsis is difficult. Hemicellulose, because of its great attraction for water, prevents overabsorption and at the same time makes a voluminous semisolid mass. The celluloses, at least those that we have examined, are not so hygroscopic and hence the mass of feces they form is apt to be more solid and friction producing.

In what way do volatile fatty acids, and perhaps other products of the chemical degradation of cellulose and hemicellulose, act? On this point we have no experimental evidence. However, it has been shown by the German observers, Bardth *et al.*,<sup>7</sup> that these acids fed to dogs hasten the evacuation of the bowels. Presumably their presence in the lumen or the wall of the colon stimulates peristalsis or tonicity. Although indigestible residue stimulates the upper intestinal tract as well as the colon, as shown by the shorter period of time that cellulose-containing foods require to pass through the upper intestinal tract, nevertheless it reaches the colon or rather the terminal ileum, where the bacterial flora is prolific, before it is broken down. Thus the stimulating split products of cellulose and hemicellulose are liberated only in the terminal ileum, cecum and the ascending and transverse colon and these are just the areas where stimulation is most needed.

We believe that there are certain acids in some of the fruits that act in much the same way as the split products of intestinal residue. We refer to the acids of raw apple, the juice of the prune and fig and other fruits.

#### IS IT NECESSARY TO ADD INDIGESTIBLE RESIDUE TO THE NORMAL DIET?

There are few constipated individuals among the well-nourished and obese. It is the asthenic, undernourished woman who is most apt to be constipated. This is explainable by the increased amount of material that the well-nourished

individual eats. His total food mass is much larger. There is no doubt in our minds that rarely would an individual be constipated who is given a liberal diet of vegetables and fruits. To our classes in dietetics we teach that the normal person should consume from  $\frac{3}{4}$  to 1 pound of vegetables, and an equal weight of fruit daily. On such an intake of bulky foods, constipation is rare and no addition of a concentrated residue is needed.

As we have pointed out, there are no analyses of the common foods which state the content of cellulose and hemicellulose. Our analyses of such vegetables as peas, carrots and cabbage suggest that these contain between 2 and 3 per cent of cellulose plus hemicellulose. A pound of such vegetables would contain approximately 10 Gm. of cellulose plus hemicellulose. It is of interest that this amount of indigestible residue was the amount found to be quite effectual in our normal subjects. Finally, we believe that indigestible residues in proper amounts of the *proper chemical composition and finely divided* can do no harm even if taken promiscuously by the general population. Too much emphasis cannot be placed upon the qualitative composition, for we have found residues high in lignin and cellulose but low in hemicellulose, which are frankly constipating and irritating to the rectum. In normal human subjects stools from such substances were passed with difficulty and were blood-flecked. This undoubtedly accounts for many instances of fecal impaction recorded in the literature and the disagreement among clinicians as to the merit of adding residue to the diet.

In the last one hundred years the use of sugar has reached the point where it accounts for 25 to 30 per cent of our calories. The same is true of white flour. Both of these materials are completely absorbed without residue. Before the advent of manufactured sugar and white flour, the ingestion of carbohydrate was invariably accompanied by considerable quantities of cellulose and hemicellulose. We are firmly of the opinion that the best way to take cellulose and hemicellulose is to eat it in the natural state, that is, from vegetables and

whole grain cereals. But we believe that there is a use for concentrated indigestible residues which can be given to individuals who cannot or will not take enough natural foods to obtain bulk. Again, there are others who have mild pathological conditions which would be greatly benefited, symptomatically at least, by giving materials which cause the stool to be more voluminous, pliable and easily evacuated.

#### CLINICAL EXPERIENCE WITH BEET PULP

One of the basic reasons for our interest in the indigestible residues obtained from agricultural by-products was the hope that we might discover some that would be economically available to the general population. Those materials now put out by the drug houses are very expensive and the great mass of our dispensary patients cannot afford to purchase them. Bran is cheap but in the form that it should be used, namely, when pulverized, it is not widely available, and from the qualitative aspect is far from an ideal material.

Much of the criticism raised against bran and other rough materials is due to the hitherto unrecognized facts (1) that lignin is the material which makes indigestible residue brittle, hard and injurious; (2) that certain indigestible residues are more hygroscopic than others; (3) that the size of the particles of indigestible residues is of great importance, particularly if the residue contains much lignin, or to a less extent, cellulose. The hemicelluloses are so hygroscopic that they can hardly be irritating. If one eliminates those indigestible materials that contain lignin and chooses only materials which are high in hemicellulose and hygroscopic as well, there are no objections to using these indigestible residues even in cases of ulceration of the gastro-intestinal tract. In fact, they are much safer to use than whole vegetables.

Chemically, beet pulp is composed of 34 per cent cellulose and 29 per cent hemicellulose with insignificant amounts of lignin. The ideal indigestible residue, it seems to us, should contain 10 or 15 per cent cellulose and 50 per cent hemicellulose. But of all the products we investigated beet pulp

seemed to us to be closest to this ideal. When it absorbs water, it forms a soft bulky mass similar to that formed by agar. It can be purchased at a very cheap price and is easily washed, dried and ground. We obtained beet pulp from the wholesale dealer, washed it overnight in hot water, dried it in a warm air dryer and ground it fine enough to pass through a 20-mesh sieve. This material is not disagreeable to taste, and by most of our subjects and patients is preferred to bran or agar. When exposed to water, it increases its volume about four-fold.

It has been used by one of us (T. B.) in the gastrointestinal clinic for the past three months. Any case where constipation predominated, whether pathological or functional, was given beet pulp in amounts of 1 or 2 tablespoonfuls a day. We have used it in duodenal ulcers, cholecystitis, so-called "spastic" colitis, hypotonic colon, rectal constipation, mucous colitis, granulomatous stricture of the rectum, gastroptosis, and individuals who have been chronic laxative users. Our experience has not been extensive but the results are more satisfactory than we have obtained by the use of agar or any of the types of emulsified mineral oils. Almost all of the cases were women. We had no control over the actual size of the stools passed, but were dependent entirely on the statements of patients. There is no subject in the field of medicine on which the public is more misinformed than its ideas regarding the normal size of the stool. Why is it that the human race feels that a daily *large* stool is the only satisfactory habit? Those of us who have weighed hundreds of stools of normal people know that some days a normal stool weighs 50 Gm. and other days 250 Gm. But even realizing this ignorance on the part of the average man or woman, nevertheless, the fact that there is the strong instinct for a daily evacuation seems to us a fact that cannot be overlooked. So even though we have not checked the patient's statements by actually weighing the stools, the fact that these individuals taking beet pulp are much more satisfied with their stool evacuation than when they are taking cathartics or mineral oil, seems to us good.

evidence of its efficacy and we believe that the material derived from a vegetable, replacing mineral salts, vegetable cathartics, is a real therapeutic accomplishment. Whether patients will continue to take it day in and day out or whether it will be necessary for them to do so, remains to be seen. Certainly the cost of this material is very little indeed.

In conclusion, we have tried to outline our past work and to give some of the deductions we have arrived at through careful study of the chemistry and behavior of the indigestible residue used in human diets. We have pointed out the characteristics of the ideal type of indigestible residue that can be added to the diet of those individuals whose stools need increased bulk. And it should be emphasized that residue constitutes not so much an addition, but rather a supplement to the diet deficient in normal sources of residue. We have in beet pulp a material which although not quite ideal, is easy to obtain, very reasonable in cost, and thus far in our experience satisfactory in the results that it has given.

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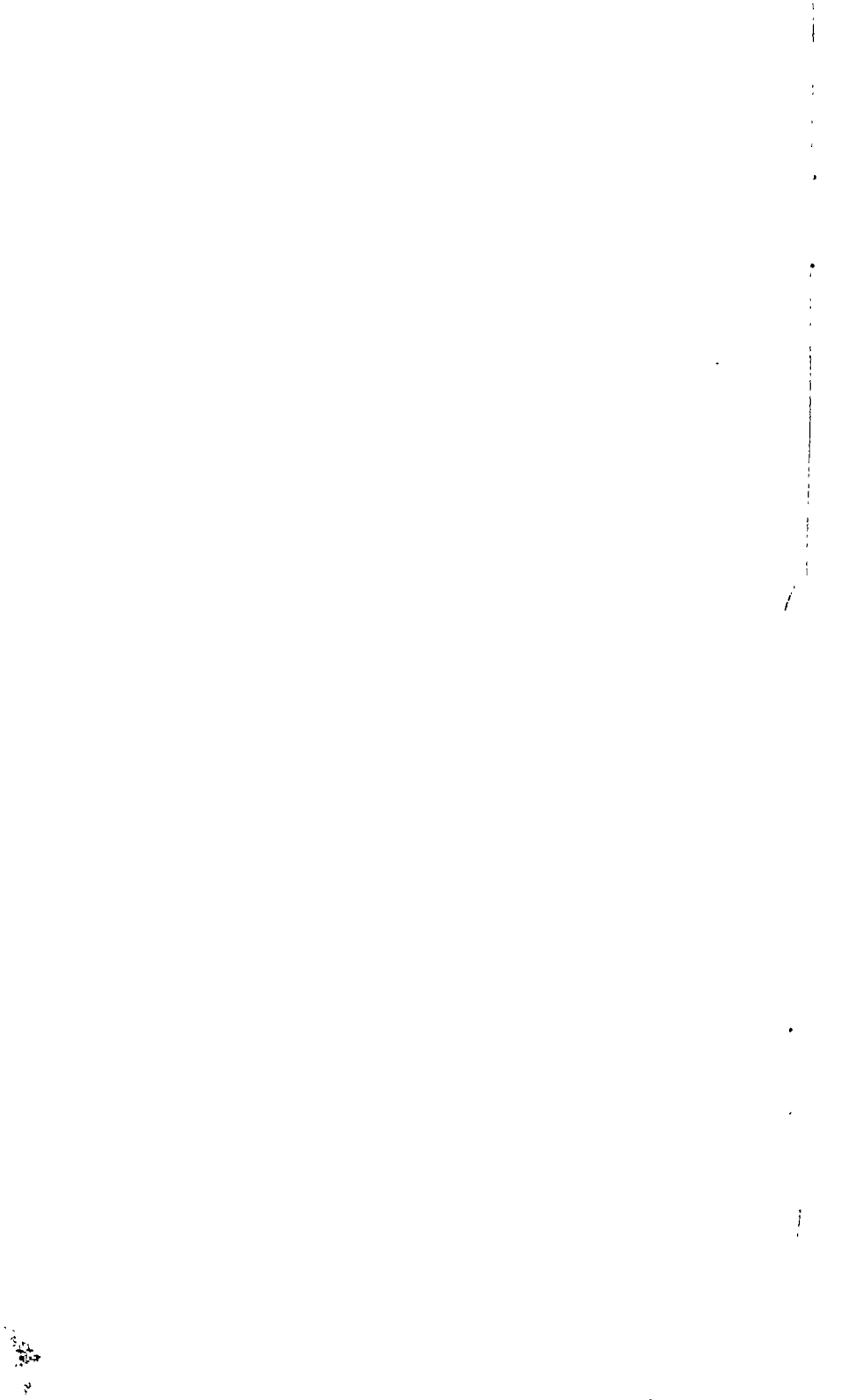
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#### PEPTIC ULCER

THE disease of peptic ulcer cannot be exemplified in all the variety of its manifestations during the progress of the characteristic clinical course by the immediate status of a single case. The following medical history is of an instructive case of peptic ulcer:

The patient is a housewife, aged fifty-six years, who had complained of hyperacidity or heartburn for fifteen years, and had "lived on milk of magnesia and soda." Heartburn had recurred in periods and came on two hours after eating. For the previous six weeks there had been continuous and increasing gastric discomfort, with much eructation having a foul taste, "like bad eggs." There was nausea occasionally, and vomiting once. The weight had been stationary at 140 pounds. Physical strength was good. Sleep was disturbed by gastric discomfort. The pain was general in the upper abdomen, much lessened by taking food, and insistently described as hyperacidity. Without adequate fruits and vegetables in the diet, the bowels were constipated. The stool was natural and there was much intestinal flatulence. The patient had had three children, and had passed a normal menopause. An ovarian cyst had been removed in 1911 and later, because of an obstructed ureter, the right kidney was removed. Constipation began then and increased.

The patient had just returned by automobile from her summer home in the north, and over the week-end prior to examination became acutely worse, with increased general distress, nausea and vomiting.

Physical examination showed a woman of average stature, asthenic constitution, weight 141 pounds, temperature normal, blood pressure 124/88, pulse 92. The ocular and body reflexes were unaltered. The teeth showed many fillings and several extractions, with poor posterior occlusion. The tonsils were moderate in size, ragged and without present inflammation. No glands were palpable. The heart and lungs were normal. The arteries were not palpable. The abdomen was flat, soft and without muscular rigidity or tenderness. There was a low midline operative scar and also one in the right upper quadrant. Visible gastric peristalsis passed from left to right below the umbilicus and there was marked succussion.

Roentgen investigation showed extreme gastrectasia with much retained content, and the pylorus was obstructed. There was a perfect contour to the prepyloric area. After adequate lavage a second opaque meal showed the deformed duodenal bulb and a perfect pyloric isthmus.

Analysis of the aspirated gastric contents showed a 60 per cent (Tophen) free hydrochloric acid and 90 per cent (Tophen) total acid.

Blood study: hemoglobin, 84 per cent; red blood cells, 4,790,000; white blood cells, 10,200.

Urinalysis: specific gravity, 1.035, acid; albumin and sugar, negative; no acetone. Microscopic examination was negative.

Stool analysis was not notable and the guaiac test for occult blood was negative.

The patient was hospitalized and operative interference was anticipated. The immediate treatment consisted in decompression of the stomach by continuous siphonage with a nasal catheter, antacid medication, intravenous glucose and subdermal saline. After the first day, frequent bland feedings were allowed with aspiration of the residue prior to each feeding. Gastric comfort was promptly secured and soon there was evidence, from lessening aspiration, although with larger feedings, that motility was improving. So much improvement occurred in a few days that the operative indication seemed

doubtful. After ten days the patient became ambulatory and returned home. Antacids were continued, diet was increased and living habits restricted to a safely normal amount of activity and rest, with careful regularity.

The subsequent course was one of continued improvement. Roentgenological review showed the stomach of normal size and motility. The patient improved in general health, weight and strength. All discomfort disappeared and the abdomen became normally "silent."

This case illustrates the recurrent periods of duodenal ulcer activity over a period of years with increasing disturbance, generally relieved symptomatically by antacids, until the pyloric embarrassment brought on a chronic stasis. Finally in a period of acute exacerbation, acute edematous swelling stenosed the pylorus completely. Medical treatment corrected this reaction, restored the gastric motility and a regulated manner of living and eating has since maintained this patient in a state of good health.

Peptic ulcer, both the disease syndrome and its characteristic lesion, is wholly a medical condition. Surgery has no place in the treatment of peptic ulcer until some secondary anatomical change has occurred to disturb gastroduodenal function in a fixed manner. It may seem a subtle distinction to speak of the disease of peptic ulcer and its characteristic lesion separately. The conception is, however, extremely important. The healing of the lesion is the immediate and direct interest in treatment, but is not to be confused with cure of the functional disorders which constitute the disease. Neither can surgical attack upon the simple lesion cure the disease. Surgery cannot expect to achieve by any alteration of natural anatomy a restoration of disordered function, which is the basis and not the result of the simple lesion. The symptoms of peptic ulcer are chiefly pain and its associations, and they are due to the lesion and not to the underlying functional derangements. This constitutes a grave danger to the clinical handling of the disease as relief of the pain and the restored comfort may be secured even before the lesion is healed and

certainly before normal function is restored. This relief is erroneously taken as a criterion of cure.

Experimental and clinical studies have arrived at a conclusive justification of the term "peptic ulcer" for the chronic round ulcer which occurs in the stomach and duodenum. The acid pepsin secretion of the stomach accomplishes the excavation and the acid effectively prevents healing, but not unless their physiological regulation is disordered and malconditioned. The gastric secretion in its qualitative characteristics is normally a natural element to the gastroduodenal mucosa, and it follows that some derangement in gastric physiology is necessary to create for the secretions such a dominant place in the development of the ulcer lesion.

The disease of peptic ulcer is fundamentally an alteration in the function of the gastroduodenal segment into an unphysiological status, which permits the development of and, by continuance, maintains the localized lesion of round ulcer, which is in fact only one of the abnormalities of the entire disease. The ulcer lesion is the end-result of the intraluminal chemical conditions produced by the malconditioning of secretion. This unnaturally increased activity of the gastric juice results from varied somatic reflexes and from habit influences. These and their sequence of physiological disorder are the factors which induce the chronicity of round ulcer. The abnormal chemical status allows at the site of an injury, which would otherwise heal promptly by reason of the intrinsic native health of the tissues, the progressive localized destructive excavation of the wall of the stomach by necrosis and digestion, creating according to location either duodenal or gastric ulcer. Healing is prevented by the prolonged secretory activity of the stomach. The failure of the healing processes in the affected tissues are not due to their pathological absence nor to their diminution but rather to interference with their action. The balance between the interference and the native healing varies in each case and accounts for the variations in the lesion and clinical course of ulcer. The fallacy of the conception that the immediate agent or reason for the injury

to the mucosa is also the cause of the continuance and extension of the ulcer lesion has impeded the understanding of other factors and seriously misdirected the efforts of both medical and surgical therapy. It was stated long ago by Cohnheim that "there must be, in addition (to the initial defect) an unknown something which prevents the healing of ulcer." It is therefore necessary to discover in man the influences which, as continuing factors of chronicity, affect the segment and alter its function. Only by correction of these factors can the physiology of the ulcer-bearing segment be restored in the manner to stop an otherwise recrudescient lesion and effect an actual termination of the syndrome.

It is the abnormal conditioning by factors existent in the somatic status, and by the psychic and habit reactivity to extrinsic factors which creates the background for abnormal secretion. Abnormal influences upon the body of the stomach, the pylorus and the duodenum cause a failure in the normal harmony of the activity of the gastric glands and of gastric motility to the needs of digestion. Continuing effective secretion is the intragastric result of the factors of chronicity and is the proved essential of primary peptic ulceration. The classical conception of hyperacidity as strong acid must be modified. A persistent and effective acid-pepsin secretion should be meant, if the term hyperacidity continues to be used. The acid may have a high titer as is usual with duodenal ulcer or may be at a normal level or less as with gastric ulcer. Gastric secretory activity has lost its normal conditioned restriction to the digestive phase of the digestive cycle and there no longer exists the interdigestive period of functional rest for the gastroduodenal segment. It is the prolonged or persistent time factor of secretion which is to be considered as the essential meaning of hyperacidity. Without this abnormally extended time factor of gastric acidity the ulcer lesion and acute injuries to the mucosa will heal. The native reparative faculty of the tissues is unimpaired and its failure is not a factor in the development of the lesion. Healing fails only when hindered by these persisting abnormal influences. It is probable that all

persons frequently suffer such transient mucosal injury with casual or no symptoms. With, however, chronic malconditioning of gastric function the same accident will invite a continuing process of excavation and, when continued acidity of high titer is promoted as in the reflex pyloric syndrome, the cratering process in the duodenum may be initiated without other initial accident to the mucosa. The gastropyloroduodenal reflex hypertonus produces pyloric hypertension, gastric hypertonus, hypermotility and hyperacidity. Duodenitis may result from the vigorous and prolonged bathing of the duodenal bulb by a gastric secretion of high acid titer.

The impairments of gastric function result from the habitual, often unrecognized, violations of the reasonable and accepted requirements of health. These irregularities induce secretory confusion or nonconditioning and abolish the essential normal cycle of gastroduodenal function. Irregularity of eating, indiscreet diet, abuse of condiments, beverages, alcohol, tobacco and confections, with inadequate bodily rest contribute to that end-result. These factors of malhygiene may and often do have associated extragastroduodenal abdominal disease, appendicitis, cholecystitis, colitis and pelvic disease, which reflexly disturb pyloric function. Gastroduodenal hypertonicity with its accompaniment of nonconditioned hypersecretion results. As the hypermotility of the stomach increases and the titer of the gastric content rises, a high acidity is superimposed upon the prolonged time factor. The duodenal bulb is irritated, becomes spastic, and reflux of the neutralizing alkaline duodenal contents is prevented. Gastric ulcer occurs when hypotonicity impairs gastric motility and destroys the normal digestive cycle allowing the continuous activity of the secretions. To be effective in initiating the ulcer lesion any accidents to the mucous membrane must follow upon this functional disorder. These functional disturbances allow continued excavation of the ulcer crater until their correction is secured. This may be achieved by medical management.

Peptic ulcer has a very definite life history, progressing.

although with varying speed, through a succession of pathological changes. The functional derangements succeed, during the life history of the lesion, from first, when the pylorus is only functionally disturbed or the stomach alone is only functionally deranged, to the later stages when the stomach is organically impaired and finally when the pylorus becomes organically obstructed. Progress of the gastric lesion gives increasing callus accumulation, perigastritis and a penetrating crater often enlarging to be an accessory pocket. The duodenal lesion may progress similarly and either lesion may directly or by perigastritis involve the pylorus, causing stenosis by edema, cicatrix or peripyloric involvement. These organic embarrassments of function fix the immediate factors of chronicity beyond any expectation of medical readjustment. They require surgical interference, chiefly for the purpose of restoring motility. Again it may be emphasized that attack upon the organic manifestations of the disease of peptic ulcer is not the correction of the essential factors.

The medical or surgical status of an ulcer may, with our present facilities of investigation of the stomach, be determined adequately. The particular phase of the evolution of the lesion as it is presented for treatment can and should be determined. The recognized facts concerning peptic ulcer may be arranged to present in an analytical perspective the progression in the chronic lesion, which cannot be treated properly upon merely its generic diagnosis as ulcer, but only after its current attributes are understood. It is more important to know of any associated intra-abdominal disease than of focal infection outside the abdomen, and the investigation of the gastro-intestinal tract and of the abdomen must be complete. The surgery of simple chronic ulcer is more likely to be of the appendix, gallbladder or pelvic organs than of the gastroduodenal segment. In many cases, removal of the appendix is necessary and occasionally removal of the gallbladder. The decision for such interference is made with full roentgenological evidence and clinical observation. Medical treatment is indicated so long as the physiological derangements



remain independent of the localized ulcer lesion and direct surgery becomes indicated only when the structural change mechanically fixes the impairments of gastroduodenal function. Medical failure, so-called, can no longer be an adequate surgical indication, although it may often indicate the presence of some organic factor requiring surgery. This, however, must be defined in each case and, until it is, the possibility remains of inadequacy in the manner of medical management as outlined and followed. Surgery may not be done merely because of a sense of medical hopelessness. Also the social, economic and intellectual status of the patient may not constitute an indication for surgical interference when by analysis of the clinical and roentgenological factors, the lesion presents no other surgically removable organic sequelae. Neither does fear of cancer constitute a surgical indication until adequate study discloses definite or ambiguous cancerous characteristics in the lesion.

The medical problem of ulcer is to correct and disestablish the factors which promote the development and progress of the ulcer lesion. Medical treatment is essentially the removal of the factors of chronicity and is directed, first to the healing of the lesion, next to improving the physical status of the patient and finally to curing the disease by restoring and maintaining a properly conditioned and cyclic function to the gastroduodenal segment. The quiescent interdigestive phase of gastric function is essential to healing and must be provided and restored. The lesion of peptic ulcer will heal with the removal of the interfering factor—the continued acid bath of excessive secretion. Neutralization will accomplish this and can be done with the simplest of antacids which may be used adequately, yet adjusted to avoid alkalosis. The accident of alkalosis indicates an indiscriminate excessive use of alkalizing rather than neutralizing agents. Gastric stasis may be relieved by lavage and prevented by dietetic measures. Diet seeks to meet several contingencies. It should stay within the impaired motor capacity of the stomach and not prolong the digestive period; reduce gastric acidity by avoid-

ance of acid and stimulating foods and by emphasis of bland foods which absorb the secretion; achieve adequate general nutrition; and maintain regularity in the digestive cycles. It is apparent that no single menu can be categorically assigned as the diet of ulcer. Initially the alternation of feeding and antacids, by absorption and counteraction of the gastric secretion, will provide the opportunity for healing of the lesion. This will be prompt under such favorable conditions. Treatment of the lesion by an ambulatory régime will avoid the implication that the relief of pain and other symptoms by the same care during a relatively brief period in hospital is the cure of the disease. After the lesion is healed or definitely started toward that end the essential restoration of the functional status of the gastroduodenal segment must receive continued attention. This entails a careful rearrangement of the patient's habits of living, and may be achieved best with the ambulatory régime. Although the ulcer lesion may heal promptly, the functional disturbances which constitute the disease of ulcer show a dominant tendency to persist and to exaggerate with unfavorable hygienic and health episodes. Reconditioning of secretion may be accomplished easily, in the absence of reflex interference of extragastric intra-abdominal disease. A vacation may allow it, but return to old habits of work and living will as easily reinstate the confusion of function. Reconstruction of the patient's habits of life must be secured in some permanent manner. Since the whole of the patient and the manner of his life must be considered, very serious doubt is cast upon the claims of any of the forms of specific ulcer therapy now in vogue. Upon the premises outlined above for the genesis of ulcer it is difficult to conceive of a conclusive restoration of normal physiology being established by any manner of injection therapy or specific oral administration regardless of their effects upon autonomic balance or tissue reactivity. These specific remedies are in the main urged for the healing of the lesion.

The accidents of ulcer, perforation or hemorrhage, are neither inevitable nor usual steps in the life history of ulcer.

Perforation to peritoneal surfaces requires immediate surgical interference. Delay is disastrous. Hemorrhage remains a medical problem unless associated to some anatomical sequelae of the simple ulcer lesion. Hemorrhage occurs from the opening of a vessel by reason of the excavating activity in the ulcer lesion. Hemorrhage can be treated best by prompt introduction of measures to permit the reparative processes to be effective—by control of acid peptic activity with antacids and selected food. Extended fasting and narcotics leave the abnormal secretory factors of the ulcer process uncontrolled. This counteracts the normal hemostatic reactions at the bleeding point. Surgery is indicated when the activity of the ulcer is encouraged by organic complications. Repeated hemorrhage may indicate in fact such a status but this should be demonstrated before recourse to surgery.

With ideal medical treatment, to which there are many obstructions, simple chronic ulcer will not advance into surgical complications. Medical diagnosis is improving and advancing the recognition of ulcer. Medical management is gradually freeing itself from the classical régime predicated upon the late, originally described, status of ulcer which has already advanced into a surgical condition. Treatment is now based upon the factors involved in the genesis of the disease and development of the lesion. Surgical technic continues to achieve more successful correction of the complicating sequelae of the ulcer lesion. It is incumbent upon the physician to determine the transition or the status of ulcer with some fixed anatomical factor of chronicity which requires surgery.

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### THE DIAGNOSIS OF THE STONELESS GALLBLADDER

THE term "stoneless gallbladder" includes acute cholecystitis which may or may not develop into an empyema or hydrops of the gallbladder; chronic cholecystitis; cholesterosis (strawberry gallbladder without stone); typhoid carrier's gallbladder; and papillomas of the gallbladder. In general it may be said that, with the exception of acute cholecystitis, the most difficult problem for the physician when dealing with these patients is in the establishment of the correct diagnosis.

The importance of recognizing the stoneless gallbladder is well appreciated by reviewing its high incidence. Graham, Cole, Copher and Moore<sup>1</sup> in their book concluded that 24 per cent of the adult population have gallstones and that an equal number have cholecystitis without stones. This suggests that 20 to 24 per cent of the adult population have potential stoneless gallbladders which may give rise to active symptoms at any time. The first sentence in a new book on the gallbladder by Rehfuess and Nelson<sup>2</sup> reads, "We now realize that gallbladder disease is the commonest cause of upper abdominal trouble." In 612 routine postmortem examinations at the Mayo Clinic Mentzer<sup>3</sup> found pathological evidence of cholecystic disease in 66 per cent of the cases. Only 8 per cent of the 612 patients had a primary diagnosis of cholecystitis which indicates that a large number of people afflicted with gallbladder disease may have very few, if any, symptoms.

## ACUTE CHOLECYSTITIS

Acute cholecystitis with and without stones occurred only 7.6 per cent of 848 cases<sup>1</sup> of gallbladder disease in the Barnes Hospital, and it may be safely said that the number without stones constituted a small fraction of this per cent.

The symptoms in acute cholecystitis are sufficiently characteristic so that the diagnosis can be made from the history and physical findings. The onset is usually sudden, sometimes with a chill. The attack begins in the epigastrium or right upper quadrant. The pain is excruciating or only moderately severe and may radiate to the angle of the right scapula. Ordinarily, the pain begins to subside in twenty-four to forty-eight hours and after a week or ten days the symptoms are gone. In *noncalculous* cholecystitis the pain is less severe and rarely colicky in nature. The fever is not high (100°-102° F.), and the leukocyte count averages between 10,000 and 18,000. Physical examination reveals local tenderness, rigidity, enlargement of liver, and occasionally the palpable mass of a large, tense gallbladder.

The value of a detailed film of the gallbladder region is slight, but is helpful in ruling out a renal colic from stone or in demonstrating positive gallstones. Cholecystography is of great help in perfecting the diagnosis, but should be withheld until the acute symptoms have subsided.

The occurrence of jaundice following these symptoms results from an inflammatory obstruction of intrahepatic ducts from edema, infiltration with leukocytes, etc., as shown by Graham.

The pathological changes vary from a mild redness of the mucosa to an extensive inflammatory infiltration of all the layers of the gallbladder wall complicated by hemorrhage, necrosis, or even gangrene. As the result of a partial blockage of the cystic duct by inflammatory debris or a stone the accumulated contents may develop into a hydrops (if non-purulent), or an empyema (if purulent) of the gallbladder.

## CHRONIC CHOLECYSTITIS

A majority of all cases of dyspepsia can be attributed to the chronically diseased gallbladder. Its manifestations are protean and extremely variable in intensity. The progress of most cases is notoriously slow. Alvarez reports that the average duration of symptoms was nineteen years.

The etiology of chronic cholecystitis without stones is uniformly attributed to infection by any one of many different organisms of different virulence. The mode of infection<sup>1</sup> can conceivably occur by: (1) descending infection from the liver by bacteria carried down in the bile; (2) ascending infections from the duodenum up the common bile duct; (3) hematogenous infections of the vesicle and ducts; (4) a spreading of infection to the wall of the gallbladder from the liver or an inflamed contiguous organ. The work of Graham and Peterman shows that routes 3 and 4 are the most likely.

Another type of chronic gallbladder disorder is that termed cholesterosis (strawberry gallbladder). Here yellow particles of an ester of cholesterol are present on the red mucosa giving an appearance resembling a ripe strawberry. A review of the literature shows that there is not an unanimity of opinion as to whether cholesterol is absorbed or excreted by the wall of the gallbladder to produce this condition.

Cholecystitis occurs twice as frequently in women as in men. Obesity, multiple pregnancies and middle age are definite predisposing factors.

The most reliable and consistent symptom of chronic gallbladder disease is recurrent indigestion with flatulence usually accompanied by mild pain and discomfort in the epigastrium or right upper quadrant. After a large meal, especially one with fats, these patients suffer with "bloating," upper abdominal distention and fullness, and seek relief by belching. Patients with infected gallbladders are frequently troubled by persistent constipation and become addicted to laxatives. Rheumatic and arthritic complaints are common associates. Nausea, vomiting, referred shoulder pain, deranged nervous

and cardiovascular systems may enter the picture to obscure the more common complaints.

Laboratory procedures are frequently the only means of obtaining the correct diagnosis. Of these the most reliable and universally accepted test is cholecystography. The Meltzer-Lyon technic for biliary drainage by duodenal intubation is a most helpful aid in diagnosis and in experienced hands is very accurate. Examinations of the stools, blood and gastric contents may be helpful in a differential diagnosis. A careful gastro-intestinal x-ray examination should be performed in all cases because the symptoms produced by cholecystitis, gastric malignancy, duodenitis and peptic ulcer may make a differential diagnosis difficult. Furthermore, cholecystic disease is not uncommonly associated with peptic ulcer and appendiceal diseases, the recognition of which requires study with the opaque meal.

In a fascinating study on the evolution of the radiographic diagnosis of gallbladder disease Sherwood Moore<sup>4</sup> points out how an x-ray diagnostic accuracy of only 30 per cent was raised to an efficiency of 97.2 per cent by the advent of cholecystography (the Graham-Cole test). There was also a large increase in the total number of pathological gallbladders detected. This increase was composed largely of the stoneless gallbladders and those with cholesterol or negative stones.

From these facts concerning cholecystitis without stones it is evident that: first, a large part of the population are affected; second, the symptoms may be severe but are usually vague; and third, cholecystography is the most reliable single procedure in its diagnosis.

The reliance placed on the cholecystographic diagnosis of the stoneless gallbladder requires a thorough understanding of this test. Graham has written that cholecystography is fundamentally a physiological test of the function of the gallbladder, liver and biliary tracts. Certain conditions are necessary for satisfactory visualization:<sup>1</sup>

1. The dye must get into the blood stream in a sufficient amount.
2. The dye must be excreted by the liver into the bile.
3. It must reach the gallbladder. This necessitates patent hepatic, cystic and common ducts.
4. The patient must be fasting in order that the sphincter of the common duct can divert the bile through the cystic duct into the gallbladder.
5. The gallbladder wall must be sufficiently normal to concentrate the dye.

A single defective link in this chain of events results in either faint visualization or nonvisualization.

The following is a brief description of the technic for intravenous and oral cholecystography used at the Edward Mallinckrodt Institute of Radiology.<sup>5</sup> The intravenous administration of the dye is preferred to the oral method because, in our hands, it gives more accurate results; it permits a liver function test; it produces fewer reactions and, most important, a known quantity of the dye reaches the blood stream. The oral method, however, is simpler, less expensive and quicker. It is ideally adapted for the routine investigation of the gallbladder in patients receiving a gastro-intestinal series who do not present predominant clinical features of gallbladder disease. The problem of choosing between these two methods resolves itself largely into a matter of individual opinion and applicability.

Intravenous cholecystography is directly applied to practically all patients whose symptoms and findings primarily suggest gallbladder disease. A preliminary open film of the gallbladder region is routinely taken on the day preceding the intravenous injection. If gallstones are unquestionably visualized the patient's physician is notified and the injection is cancelled.

Ampules of phenoltetraiodophthalein sodium are prepared in the Barnes Hospital pharmacy to insure the use of fresh solutions. In the preparation of intravenous solutions too much emphasis cannot be placed upon the necessity of using



absolutely clean glassware and freshly distilled water of known purity. Extreme care should be used in washing the containers, syringes, etc., free of lysol or other antiseptics which may drain into them from the sterile instrument used in their handling.

For adults the dosage is 2.5 Gm. (38 grains) of phenol-tetraiodophthalein sodium for patients weighing 138 pounds

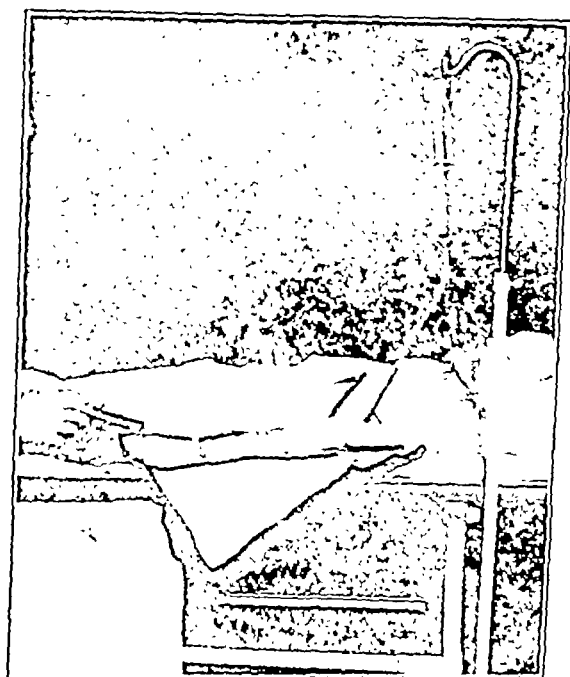


Fig. 32. Set-up for intravenous administration of phenoltetraiodophthalein sodium showing gravity flask containing 25 cc. of warm sterile saline solution (0.9 per cent). About 20 cc. of saline must first run in freely to verify the position of the needle within the vein

or over. Proportionately smaller doses are given to patients weighing less. In the preparation of a single ampule 2.5 Gm. of phenoltetraiodophthalein sodium (iso-iodeikon) are dissolved in 30 cc. (1 ounce) of hot triple distilled  $\text{CO}_2$  free water. The solution is filtered through five layers of fine filter paper and placed in a glass ampule which is sealed in the gas

flame and then sterilized in a boiling bath for twenty minutes. An ampule prepared in this manner can be safely used within a period of three weeks.

The only preliminary preparation necessary for intravenous cholecystography is that the patient receive no fluids or food after midnight on the day preceding the injection. The following morning breakfast is omitted and the dye is injected at 9 A. M. The technic of the administration is illustrated in Figs. 32, 33.

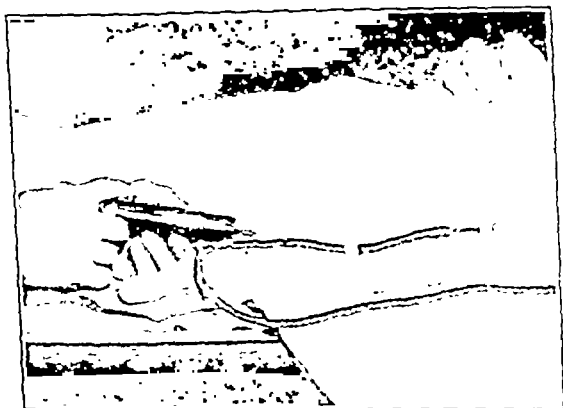


Fig. 33.—The glass syringe containing 30 cc of phenoliodophthalein sodium solution (1 ampule) is shown inserted into the rubber tubing after first sterilizing the outside of the rubber tube with alcohol. The mixture of the sterile saline solution and dye is observed by the operator as it flows through the glass adaptor fitted to the needle puncturing the vein; thus the rate of injection of the dye can be absolutely controlled and stopped with the appearance of any toxic symptoms without interrupting the flow of saline. Fifteen minutes are required for the injection of the dye. Sufficient saline is run in after all the dye has been injected to wash out the vein.

The films are made in the prone position four, eight and twenty-four hours after the injection. The gallbladder should be definitely visualized on the first film. At eight hours the shadow should have altered in size and increased in density. This capacity to alter in size is considered a measure of the elasticity of the gallbladder wall. The increased density is due to the concentration of the dye resulting from the absorption of water by the intact and functioning mucosa of the vesicle.

After the second film the patient may have food and drink including supper and breakfast. A special fat meal is not considered necessary. The final film is taken the next morning, when the gallbladder shadow has normally disappeared or has decreased considerably in size and density, demonstrating the ability of the vesicle to empty. If the gallbladder fills, concentrates the dye, alters in size and empties, as described above, it is considered normal. Nonvisualization of the gallbladder means a diseased (pathological) gallbladder. A faint gallbladder shadow indicates an impairment of the concentrating function and is somewhat proportional to the degree of pathology present. This is a treacherous sign and demands considerable experience in the viewing of cholecystograms. Sherwood Moore<sup>6</sup> has prepared an excellent summary on the radiological interpretation of cholecystograms.

For the liver function test 12 cc. of blood are removed exactly thirty minutes after beginning the dye injection. The blood is placed in a clean test tube, allowed to clot, the serum alkalized and compared colorimetrically with known standards.

The capsule method as formulated by Larimore is employed routinely for oral cholecystography. The individual dosage by mouth is 4.7 Gm. (72 grains) of tetraiodophenolphthalein. It is thoroughly mixed with 0.8 Gm. (12 grains) of pulverized agar and the mixture put into 6 stearic acid-coated capsules, 00 size.

The stearic acid serves to prevent the dissolution of the capsules by the gastric juices. As a further precaution one heaping teaspoonful of baking soda is given about thirty minutes prior to taking the capsules to increase the alkalinity of the intestines. The dye thus passes into the duodenum without being converted into the insoluble acid tetraiodophenolphthalein. The stearic acid coating is digested by the alkaline intestinal juices and, as the powdered agar becomes moistened, it swells and tends to prevent "caking" of the dye. The dye is carried to the liver by the portal circulation where it is excreted in the bile. The gallbladder shadow is produced

in the same manner as described under the intravenous method.

No preliminary preparation for oral cholecystography is necessary and it is preferable that the patient have the regular evening meal. At 7:30 P. M. the patient takes the soda in a half glass of water. Then, within the hour of 8 P. M. and 9 P. M. all 6 capsules are taken with as little water as necessary to swallow them. Food and drink except for small amounts of water are prohibited and breakfast is omitted.

Roentgenograms are made twelve, fifteen and eighteen hours following the ingestion of the capsules. After the second film the patient has the regular noon meal.

Any adequate visualization of the gallbladder without abnormalities of position, size, contour, or content (stones or papillomas) is considered normal. Very faint shadows or non-visualization associated with reactions, as severe diarrhea or early vomiting, is classed as indeterminate because loss of the dye vitiates the results. This occurs in a minimal number of cases and the test is repeated, preferably by the intravenous method.

Reactions have caused no significant inconvenience to the patients, who rest in a horizontal position for one-half hour after the injection as a precautionary measure. Hypodermic injections of 4 to 8 minims of adrenalin controlled urticaria and reactions simulating circulatory shock. Abdominal cramps and diarrhea following oral administration of the dye are best treated with codeine and paregoric.

The only definite contraindications for intravenous or oral cholecystography are severe cardiac disease and patients with very low blood pressure. From a physiological viewpoint patients with acute liver infections, common duct obstruction or acute yellow atrophy of the liver, should not be submitted promiscuously to cholecystography. In patients with jaundice of any type the gallbladder is rarely visualized. The test should be deferred with patients having high fever, severe cachexia, or marked dehydration.

While cholecystography is invaluable in the diagnosis of

stoneless gallbladders it should be emphasized that a pathological cholecystogram is not a sufficient reason for cholecystectomy. Several writers have called attention to the unsatisfactory results following cholecystectomy on patients whose gallbladders revealed only minimal changes. Graham and Mackey<sup>7</sup> report that "In the absence of severe pain the beneficial results to be obtained by cholecystectomy in cases of a stoneless gallbladder are likely to be unsatisfactory in approximately 40 per cent." The determination of how much a patient's symptoms are due to the gallbladder in a case of minimal disease necessitates an extremely thorough study for sources of other trouble before resorting to operation. It is well to remember that cholecystitis without stone is a disorder the severity of which varies widely and includes the borderline area between functional and organic disease. Kirklin and Blake<sup>8</sup> point out that "However valid the cholecystographic signs of impaired function may be of disease of the biliary tract, they will not determine whether the disorder is transient or chronic, mild or severe, or whether it is the cause of the patient's chief complaint, and determination of these matters rests solely with the clinician. In short the roentgenologist and the clinician are obliged to cooperate."

#### SUMMARY

In spite of the widespread occurrence of cholecystitis without stone there is no lesion in the abdomen that requires a more painstaking study of the patient's history and cholecystograms. Such an illusive diagnosis must be confirmed further by the differential elimination of other disorders in the abdomen.

The author expresses his appreciation to Dr. Sherwood Moore and Dr. Glover H. Copher for their help and suggestions.

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## CLINIC OF DR. ALFRED GOLDMAN

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#### DIAGNOSIS AND TREATMENT OF PULMONARY BLEEDING

PULMONARY bleeding is one of the most important symptoms of pulmonary disease and certainly the most striking to the patient. For the proper handling of a case of pulmonary hemorrhage, it is essential first of all to make a correct diagnosis. While the majority of cases of pulmonary bleeding is due to tuberculosis, careful study has shown that many cases have been erroneously diagnosed. The routine use of lipiodol and bronchoscopy in doubtful cases has been particularly valuable. In this discussion the chief consideration will be that of bleeding from the lungs and bronchi.

From the standpoint of diagnosis it is important to distinguish between hemoptysis and hematemesis. This is usually easy but there are times when blood from the lungs is swallowed and more rarely vomited blood may be aspirated and then coughed up. The history of previous or subsequent pulmonary trouble is important. In the absence of a suggestive history, as when hemoptysis or hematemesis occurs as an initial symptom, the character of the blood is important. Pulmonary blood is usually frothy, bright red in color, alkaline in reaction, the coagula are usually small and there may be mixed mucopus. Gastric blood is usually dark, clotted, may be mixed with particles of food and is often acid in reaction. The patient usually turns pale and may faint and then has hematemesis, while in hemoptysis the bleeding occurs first and then pallor and faintness ensue.



Local conditions in the nose, throat and larynx must always be considered in supposed cases of pulmonary bleeding. These are more properly taken up by the rhinolaryngologist but should be mentioned here. The *nose* may be the seat of epistaxis. In the *mouth*, a gingivitis may be the source of the blood. Adenoids occasionally bleed. In the *pharynx* peritonsillar abscess and varicosities at the base of the tongue may cause profuse bleeding. In the *larynx* the following conditions may cause bleeding: luetic, tuberculous and malignant ulcers, injuries, varicosities, angioma and any acute laryngitis. In the *trachea*, luetic or malignant ulcers, foreign bodies, varicosities, congestion from pressure of an aneurysm, an enlarged thyroid or tumor, irritant gases such as chlorine or mustard.

Practically all of the above mentioned causes for bleeding may be directly visualized by the laryngologist and bronchoscopist.

Bronchopulmonary bleeding may be classified as follows:

(A) Diseases of the lungs and bronchi:

1. Pulmonary tuberculosis,
2. Bronchiectasis,
3. Broncholithiasis,
4. Pulmonary abscess,
5. Pulmonary gangrene,
6. New growths,
7. Injuries of the lung,
8. Pneumonia,
9. Pneumoconiosis,
10. Fungus infections,
11. Foreign body,
12. *Fusospirochetosis*.

(B) Diseases of the heart and vessels:

1. Mitral stenosis,
2. Thromboses and emboli from cardiac disease,
3. Emboli from phlebitis,
4. Aortic aneurysm rupturing into the lungs, bronchi or trachea.
5. Hypertension.

(C) Diseases of the blood.

(D) Vicarious menstruation.

(E) Hemoptysis in the healthy.

## (A) DISEASES OF THE LUNGS AND BRONCHI

1. **Pulmonary Tuberculosis.**—Every case of frank pulmonary bleeding should be considered as pulmonary tuberculosis unless proved otherwise. There are three types of bleeding in tuberculosis. In the early stage, the hemorrhage is usually caused by a local inflammatory hyperemia, the amount of blood is small, usually mixed with sputum. Later, as softening of the lung takes place, small vessels may be invaded and rupture takes place. This may give rise to a profuse hemorrhage. In the last or cavitation stage, the severest type of hemorrhage occurs due to rupture of a miliary aneurysm in the wall of a pulmonary artery. If this lies in a large cavity, fatal hemorrhage may take place. This fortunately is rare and recovery may take place from the severest type of hemorrhage in tuberculosis. Fishberg states that less than 2 per cent of bleeding consumptives die from hemorrhage directly.

The diagnosis of tuberculosis is usually obvious. The previous history, past and family, the physical examination, study of the sputum, x-ray are all of equal value. It must be remembered that with severe bleeding, very little examination may be possible and accurate diagnosis may have to be deferred. In doubtful cases, a tuberculin test may be of value, especially when negative. The age of the patient is of value, hemorrhage in tuberculosis occurring in the young and middle-aged. There is a definite small group in which the findings are so minimal that only subsequent developments can assure the diagnosis. These cases must be considered as tuberculosis in the absence of some other satisfactory explanation. Other diagnostic features will be taken up in the consideration of other causes of bleeding.

2. **Bronchiectasis.**—Hemorrhages are very common in bronchiectasis, occurring in 50 per cent of the cases. The blood is usually well mixed with sputum but in some cases, there may be severe bleeding, practically never fatal, however. Differentiation from tuberculosis is usually easy. The site of the bronchiectasis is usually basal but the occasional case of apical bronchiectasis will be confusing and more diffi-

cult of differentiation from tuberculosis. The study of the sputum is the chief differential point. The routine use of lipiodol is indicated in all cases of pulmonary bleeding where diagnosis is obscure and where the necessary manipulation of the patient in introducing the lipiodol will not be harmful. Often bronchiectatic areas which have been completely overlooked by physical examination and x-ray have been visualized with oil. This is particularly true in cases where the diseased lung field is covered by the heart shadow. It must be remembered that bronchiectasis is common in pulmonary tuberculosis. Many of our bronchiectatic cases have been bronchoscoped for direct visualization of bleeding areas.

3. **Broncholithiasis.**—The most common symptom of broncholithiasis and pneumolithiasis is bleeding. Bleeding is usually mild but at times may become fairly severe. It is rarely fatal. The blood may precede the coughing up of a stone or may occur without the expulsion or may follow the stone. One of my patients who has coughed up approximately 25 stones in the past three years was able to foretell the passing of a stone. The initial symptom was pain in the anterior chest. This was followed by a rather profuse hemorrhage and then a stone would be coughed up. Shortly after the expulsion, the patient was free of all symptoms and remained asymptomatic until the next attack. The diagnosis is, of course, dependent on the history, but one must question the patient specifically about the presence of "stones" in the sputum. A tentative diagnosis may be made on the basis of numerous calcifications seen in the x-ray plate. There are occasional cases in which no broncholiths are visible in the x-ray. Stones have been expelled following induction of artificial pneumothorax in cases where no stones had been previously expectorated. Lipiodol may show the presence of a blocked bronchus. Bronchoscopy may show the stones in the bronchial lumen or perforating into the bronchus and the stones may be easily removed.

4. **Pulmonary Abscess.**—Abscess of the lung often shows bloody sputum usually well mixed with pus. Frank bleeding

may be present. The diagnosis is based on the symptoms of a pyogenic infection, fever, cough and foul purulent sputum. The physical signs are those of cavity but are not readily made out unless the abscess is large and close to the periphery. The x-ray shows a rarefaction with a fluid level. Apical abscess may be difficult to differentiate from tuberculosis. The sputum examination for tubercle bacilli is important. Elastic tissue is present in lung abscess. Clubbing of fingers is common in pulmonary abscess. Lipiodol may be necessary to distinguish from bronchiectasis. Lung tumors may be secondarily infected and give symptoms of lung suppuration.

5. **Pulmonary Gangrene.**—Bleeding in gangrene varies from a small amount of blood to very large hemorrhages. Indeed, fatal hemorrhages are not infrequent. The diagnosis is based on the symptoms of cough and sputum of very offensive odor. Large amounts of lung tissue may be expectorated. Most cases progress to a rapid death, although an occasional one survives.

6. **New Growths.**—Cancer of the lung is one of the most common causes of hemorrhage in people past fifty. Bleeding may be absent, may be slight and may appear as blood streaks, or there may be a profuse but rarely fatal hemorrhage. The diagnosis is based on the symptoms of pain in the chest, dyspnea and hemoptysis in a person past middle life; the presence of a more or less characteristic mass on physical signs and x-ray; a pleural effusion which may contain malignant cells; the presence of malignancy elsewhere; the presence of atelectasis as evidenced by the use of lipiodol; the bronchoscopic evidence of tumor; the presence of tumor tissue in expectorated sputum; thoracoscopy may directly visualize a tumor and finally, an exploratory thoracotomy may be necessary for diagnosis.

7. **Injuries of the Lung.**—Any severe trauma to the chest wall may cause mild or severe pulmonary bleeding. Those cases in which fractured ribs puncture the lung are quite obvious. Severe bleeding may occur following blows without

fracture. In such cases, the possible inciting of an old tuberculous process must be considered, though undoubtedly bleeding may take place from the normal lung. Spontaneous pneumothorax may produce pulmonary bleeding particularly if the lung is torn. Hemorrhage may occur after attempted paracentesis of the pleural cavity.

8. **Pneumonia.**—The early sputum in lobar pneumonia is blood-streaked and later becomes rusty. Occasionally pneumonia may start out with a brisk hemorrhage. In bronchopneumonia of the influenzal type frank blood is often present in the sputum. The diagnosis is usually easy although tuberculosis must always be kept in mind.

9. **Pneumoconiosis.**—This condition is very rarely a cause for hemoptysis. Occasionally cavities occur in anthracosis which might produce bleeding. Bleeding is seen in chalicosis. The severe types of hemorrhage are usually associated with secondary tuberculosis.

10. **Fungus Infections.**—Actinomycosis, aspergillosis and streptothricosis cause chronic lung suppuration and may produce bleeding. This is usually an important symptom.

11. **Foreign Body in the Lung.**—This may cause immediate bleeding, particularly if the foreign body is nonorganic. Any foreign body may produce bloody sputum as pulmonary suppuration develops following blockage of a bronchus. Diagnosis depends on the history of a foreign body, symptoms and physical signs of obstructive breathing and bronchoscopy. The latter is very important and should always be done even in doubtful cases. Lipiodol may be done prior to bronchoscopy and may show an obstructed bronchus.

12. **Fusospirochetosis.** — Bronchopulmonary spirochetosis may cause blood-streaked sputum or mild hemoptysis. The diagnosis is made on the finding of fusiform bacilli and spirochetes in large numbers in the sputum. These organisms are often present in small numbers, as secondary or nonimportant organisms in chronic lung disease.

## (B) DISEASES OF THE HEART AND VESSELS

Mitral lesions very commonly cause hemorrhages. Some observers feel that it is probably second only to tuberculosis as the most common cause of pulmonary bleeding. While hemorrhages are usually slight, coming by diapedesis or rupture of capillaries, at times very severe paroxysmal pulmonary hemorrhages may occur.<sup>1</sup> Death from hemorrhage may occur in mitral stenosis. Infarcts form and produce dense shadows in the lung which may be difficult to differentiate from pulmonary tuberculosis. It is a well-known fact that patients with mitral stenosis often find their way to a tuberculosis sanatorium because of the bleeding. The diagnosis is dependent on a careful examination of the heart. The characteristic murmurs may be absent when the heart is rapid and a flutter or fibrillation may be overlooked. The dense shadows sometimes seen in the lung picture in mitral stenosis following hemorrhage disappear quickly and completely with improvement. Pulmonary tuberculosis is extremely rare in mitral stenosis.

Thrombi and emboli from cardiac disease and emboli from other sources cause hemorrhages of varying degrees. An infarction may be present without hemoptysis. The diagnosis of infarction is based on the history of probable presence of emboli, sudden pain in chest, dizziness, hemorrhage and physical signs of infarction. A large infarction is immediately fatal. In the lesser bleeding of cardiac congestion heart failure cells are usually found in the sputum.

An aortic aneurysm may produce seepage of blood into the bronchopulmonary tract and cause frequent bleeding. The sudden rupture of the aneurysmal sac into the lungs or bronchi causes severe hemorrhage with immediate death, a common ending in aortic aneurysm.

Occasionally, bleeding occurs from the lungs in cases of hypertension in which there is no evidence of tuberculosis. This may be due to congestion or infarction.

### (C) DISEASES OF THE BLOOD

Purpura, pernicious anemia, scurvy, hemophilia, leukemia, all may produce hemoptysis. Bleeding, however, is unimportant in these cases.

### (D) VICARIOUS MENSTRUATION

It is a well-known fact that tuberculous women are apt to spit blood during the menstrual period. Occasionally non-tuberculous pregnant women have periodical pulmonary hemorrhages which cease following childbirth. At times, apparently healthy women have severe hemorrhages during menstruation.

### (E) HEMOPTYSIS IN THE HEALTHY

Pulmonary bleeding may occur in young healthy individuals without any apparent explanation. Bleeding may recur from time to time. Many of these cases have been followed for years without developing any pulmonary lesion. Tuberculosis must be carefully considered.

### TREATMENT OF PULMONARY BLEEDING

Mild hemorrhages require no special treatment other than that of the underlying condition. In all cases of pulmonary bleeding, the patient should be reassured that it is in itself of little significance. There is considerable truth in the statement that if the patient survives the immediate effects of the hemorrhage, the prognosis from the standpoint of blood loss is good. As stated above, pulmonary bleeding very rarely causes death. However, there is much to be gained by the proper handling of a case. It is, of course, extremely important to make a proper diagnosis. Since severe bleeding contraindicates any extensive examination, diagnosis may be delayed and treatment instituted without exact knowledge of the kind and site of the bleeding lesion. It must be emphasized that pulmonary hemorrhages often stop spontaneously, so that the apparent excellent therapeutic effect of any of the numerous methods used must be interpreted with caution.

1. **General Methods.**—Absolute bed rest is indicated, but the patient should be put and kept in a semireclining position so as to facilitate the expulsion of blood and sputum. The patient is usually very apprehensive and should be calmed and assured that the hemorrhage is not serious and will soon stop. He should be encouraged to bring up the secretions in the bronchial tubes gently and with little expulsive effort. He should be allowed to move quietly in bed but not to the complete sitting position. An ordinary chest binder may help reduce the cough. The period of rest is dependent entirely on the cause of bleeding.

The use of morphine has long been a mooted question. To snore the patient under and allow him to retain blood clots and sputum is to encourage aspiration pneumonia, atelectasis or spread of the pathologic process present. However, morphine produces rest of the body, peace of mind and allays excessive cough. Severe coughing obviously encourages renewed bleeding. It is best, therefore, to give codeine first, and if this is insufficient a small dose of morphine, preferably  $\frac{1}{6}$  grain, may be given. It is usually unwise to repeat the morphine. Sodium bromide is of value in 5-grain doses.

An ice-bag to the chest is a measure of reassurance to the patient, but probably has no other real value. Swallowing of small bits of ice is usually advised.

Binding of the limbs, the arms and legs for one-half to two hours with a tourniquet and then slowly loosening the tourniquet may be of value. This is supposed to increase the thrombokinese in the blood and encourage blood coagulation.

The diet is important during bleeding. The patient should be starved for a few hours. A soft diet should be used with limitation of ingested fluids. Hot foods, tea, coffee and alcohol are contraindicated. A regulation diet may rapidly be resumed several days after cessation of bleeding.

*Artificial Pneumothorax.*—In pulmonary tuberculosis artificial pneumothorax is our most effective measure when other simpler methods have failed. It is, of course, necessary to know from which side the hemorrhage is coming. This may be very



difficult as the tuberculous lesion may be bilateral. The patient's symptoms, the physical signs, and the x-ray are helpful in the localization. In cases where it is impossible to localize the site, pneumothorax may be induced on the most likely side. Some maintain that even if the wrong side is collapsed, a favorable effect is produced on the bleeding lung. When pneumothorax is technically impossible because of adhesions, other forms of collapse therapy may be used. Phrenicectomy in conjunction with artificial pneumothorax has been of value. Plombage may stop the hemorrhage coming from an apical cavity. Finally thoracoplasty may be necessary to control hemorrhage in tuberculosis.

In nontuberculous lesions collapse therapy may also be indicated. We have stopped hemorrhage in cases of bronchiectasis and lung abscess by artificial pneumothorax. We have had a striking instance of cessation of bleeding in bronchiectasis by phrenicectomy. We have had the interesting experience on several occasions of the expulsion of an unsuspected broncholith following artificial pneumothorax for bleeding. There are certain cases of undiagnosed pulmonary bleeding in which one may be justified in inducing a pneumothorax for symptomatic relief. The compression may be immediately effective and continue so long as the lung is collapsed.

*Bronchoscopy.*—Bronchoscopy is of considerable value in the diagnosis and treatment of pulmonary bleeding. It should be used routinely in all cases of undiagnosed pulmonary hemorrhage unless there is some special contraindication. As a therapeutic measure it is of particular value in cases of foreign bodies, broncholiths and endobronchial tumors. The bronchoscopist may be able to directly treat bleeding areas in the tracheobronchial region. He may indirectly influence hemorrhage by his treatment of lung abscess and bronchiectasis. Bronchostenosis may be favorably affected.

*Lobectomy and Pneumonectomy.*—This special operation is indicated not because of bleeding in itself but because of the underlying lesion. Lobectomy is the operation of choice in bronchiectasis. In carcinoma of the lung it is the only

method of cure except in those rare cases in which an early endobronchial tumor may be satisfactorily removed by the bronchoscopist. Removal of an entire lung for carcinoma has been successful.

**2. Methods to Reduce Blood Flows and Increase Coagulation.**—There are many drugs which have been advocated for pulmonary bleeding. The purpose of the drug is either to reduce the pulmonary blood flow or to increase the coagulability of the blood. It must be said that in spite of enthusiastic support on the part of many, most of the drugs are probably valueless. However, they should be mentioned.

*Salt.*—The swallowing of a tablespoon of common table salt dissolved in a glass of water is a time-honored remedy. This is said to increase the coagulation of blood. The salt may be injected intravenously, 5 cc. of a 10 per cent solution may be used, 10 cc. of a 10 per cent calcium chloride solution may be used for the same purpose.

*Emetine.*—This may be used hypodermically in  $\frac{1}{2}$ - to 1-grain doses in place of ipecac. It is supposed to act as a hemostatic. Its value is doubtful.

*Ergot* is a very popular remedy but it actually causes a rise in the pulmonary blood pressure and should not be used.

*Digitalis* raises blood pressure in the pulmonary artery and is therefore theoretically harmful.

*Aconite* produces a definite fall in the pulmonary blood pressure and may be of value.

*Pituitary extract* while raising the systemic blood pressure lowers the pulmonary blood pressure. It may be used in protracted cases.

*Atropine* may be given hypodermically in  $\frac{1}{100}$ -grain doses with apparent benefit.

*Congo red* given intravenously was first advocated by Becker.<sup>2</sup> He gives 10 cc. of a 1 per cent solution intravenously. It is supposed to reduce clotting time, increase the blood platelets and blood fibrin content.

*Ammonium tartrate* is strongly recommended by Maltei and Escudies.<sup>3</sup> It is given daily in 10-Gm. doses for five days.

*x-Ray of the spleen* is advocated by Neddermeyer<sup>4</sup> who states that it hastens blood coagulation.

*Adrenalin* by mouth and subcutaneous injection has been extensively used with doubtful results. Ascoli<sup>5</sup> has recently advocated a method by Dr. Guiffrida in which adrenalin is injected directly into the bronchi by the intratracheal superglottic route. Three cc. of a  $\frac{1}{1000}$  solution of adrenalin diluted with 2 cc. of water is used and may be repeated in twelve hours.

*Intratracheal injection of water* is highly recommended by Pennetti<sup>6</sup> who states that it causes a reflex vasoconstriction and stops hemorrhages in the majority of cases.

*Camphorated oil* in hypodermic form, 5 to 10 cc. of a 25 per cent solution, is highly recommended and apparently stops hemorrhage.

*Parathormone* may be used intravenously in 10-unit doses.

*The nitrites* may produce a lowering of the pulmonary blood pressure and may be of value in this way. It may be used in the form of amyl nitrite or nitroglycerin and should be given in larger doses than normally used.

*Purgation* in the form of epsom salts lowers the blood pressure and may be used with benefit.

*Alum, tannic acid and lead* are of no value.

*Gelatin* best given by mouth may be used but is of doubtful value.

*Calcium salts* by mouth have long been used but have no influence on the bleeding.

*Coagulants* such as thromboplastin, coagulin, fibrogen, etc., are all supposed to increase blood coagulation but have been ineffective.

*Blood transfusions* in small amounts up to 100 cc. of blood have proved of value. Larger amounts increase the blood volume and are therefore of some danger. The question of severe blood loss must of course be considered. Horse serum may be used in nonsensitive cases.

In all cases of pulmonary bleeding it is, of course, essen-

tial to treat the underlying cause, the bleeding often being of minor importance.

### SUMMARY

The first consideration in the handling of a case of pulmonary bleeding is a proper diagnosis. The routine use of lipiodol is of tremendous diagnostic value especially in the nontuberculous cases. Bronchoscopy is also a valuable adjunct.

The treatment is primarily the proper management of the underlying lesion. The general methods of treatment are by far the most important. Bed rest, reassurance of the patient, sedation enough to control the cough and allay the patient's mind, all these measures are of prime importance. None of the drugs mentioned above are specific but they may be used in protracted cases. When all the simpler measures have failed, artificial pneumothorax should be used in cases of pulmonary tuberculosis. In undiagnosed cases of continued bleeding, artificial pneumothorax should also be used as a temporary measure.

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## CLINIC OF DR. J. J. SINGER

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### THE DIAGNOSIS AND PREVENTION OF SILICOSIS (THE SILICOSIS PROBLEM)

**Case I.**—H. M. was a thirty-one-year-old white man who entered Barnes Hospital March 7, 1932. His complaints were dyspnea, a productive cough, slight fever, night sweats and marked loss of weight. He began to notice symptoms of weakness and shortness of breath about two and one-half years ago after working in a dusty roofing factory, for four years, where gravel with a high silica content was ground for roofing material. Two months later these symptoms became more severe and patient was forced to quit work. After rest he was not improved. A productive cough developed with a thick, dark brown sputum, occasionally blood-streaked.

*Physical Examination.*—Patient pale, pupils equal, react to light; teeth poor with much caries and pyorrhea. Pharynx congested, no glandular enlargement; chest is emphysematous, diminished breath sounds throughout with fine moist râles heard here and there, no areas of consolidation noted by physical signs; heart sounds are normal; abdomen negative. Laboratory reports are as follows: no acid-fast bacilli found in sputum, guinea-pig injection was negative. Red blood corpuscles, 5,050,000; white blood corpuscles, 13,600; hemoglobin, 83 per cent. Kahn: negative and vital capacity 1370 cc. x-Ray films show a diffuse peribronchial thickening throughout resembling miliary tuberculosis. There was no

evidence of fluid in the chest pleural cavity. Patient treated symptomatically. On April 17, 1932, patient continued to be about the same as a week ago, possibly slightly improved. On April 22, 1932, physical signs and x-ray showed similar condition as before. Areas of pathological compensatory emphysema in close proximity. Fluoroscopy showed no change.



Fig. 34.—Case I. Film taken April 22, 1931. See text for description.

Patient was anxious to go home, although advised not to (discharged April 23, 1932).

*Comment.*—x-Ray taken on April 22, 1931. At this time patient had symptoms of dyspnea with occasional blood-streaked sputum and weakness. His general appearance was good. This film showed fine nodular thickening throughout both lungs, particularly from hilus to axillary area and to bases of the lung. The air content, however, is generally good; both diaphragms move well and were smooth in outline.

Film taken March 16, 1932, almost one year later, although there was no further exposure to silica dust one notes increase in the amount of density and that the nodular densities have increased both in size and intensity. The right hilus is

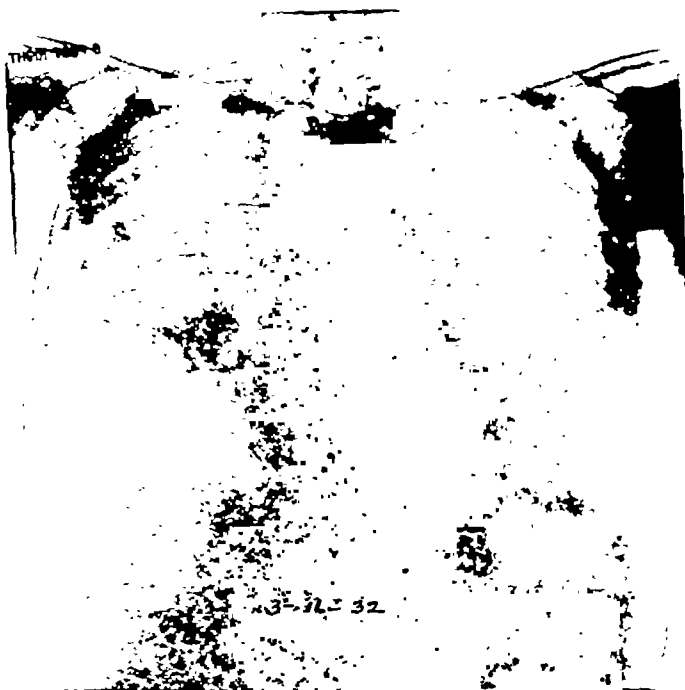


Fig. 35.—Case I. Film taken March 16, 1932. See text for description.

thickened, both diaphragms are more irregular and the general air content of the lungs is markedly diminished. With the increase of physical changes noted by x-ray and the stethoscope the symptoms increased accordingly.

Case II.—L. P., age forty-eight years, first admitted to the Barnes Hospital on October 31, 1931. His complaints were dyspnea, cough, pain in the right chest, expectoration, occasionally blood-streaked (never foul) and loss of weight. He was a steel worker between the ages of fifteen and twenty-two years. The next two years were spent in a gold mine,



## DISCUSSION

In the past five years the disease known as silicosis has become a very important problem to physicians, lawyers, and industrialists. To each of them the problem is a distinct one, but we as physicians are interested primarily in its cause, prevention and cure.

There have been numerous articles written, particularly in the last five years, regarding silicosis. Much of the work has been undertaken by the United States Government through its Public Health Service and Bureau of Mines. A fair amount of work has been requested by the industrialists.

The first mention of dust disease was by Pliny in 76 A. D.<sup>1</sup> In 1556, Agricola<sup>2</sup> published an excellent treatise which covered diseases connected with miners. Henry Stuart Willis, in an excellent monograph on the subject entitled, "Pneumoconiosis and Tuberculosis,"<sup>3</sup> gives an interesting historical review of the condition known as pneumoconiosis and silicosis from the time of Agricola till the date of the publication of his article in December of 1930. It can be readily seen, therefore, that miners and those in the dusty trades received considerable medical observation and that a certain amount of caution has been expressed to prevent the serious dangers associated with the inhalation of dust.

At the present time health hazards connected with industries in which considerable dust is present are receiving attention from physicians and sanitary engineers interested in the problem. A great improvement in the physical character of industrial plants has resulted so that silicosis, as a disease, may in the future be partly eliminated.

There is still debate among medical men, as to whether symptoms in exposed individuals are actually due to silicosis or to other pulmonary or cardiac diseases. Because of the difference in opinion this question was referred to a committee of the Public Health Association. After analyzing the various symptoms and the diseases with which the patient may be suffering, the committee offered the following definition of silicosis:

"A disease due to breathing air containing silica. characterized anatomically by generalized fibrotic changes and the development of miliary nodulation in both lungs, and clinically by shortness of breath, decreased chest expansion, lessened capacity for work, absence of fever, increased susceptibility to tuberculosis (some or all of which symptoms may be present), and by characteristic x-ray findings."

A diagnosis of silicosis depends on four important factors: (1) etiology; (2) symptomatology; (3) physical signs; and (4) roentgenographic studies. It is necessary in etiology to have the complete history of the patient's occupations at the time of the illness and in the many years preceding. It is well known that considerable exposure to silica may be required to produce an incapacitating condition. Dr. Lanza,<sup>4</sup> formerly of the Public Health Service, in a discussion of the silicosis problem, states that two years is usually the shortest period of the development of the disease, but usually it is much longer. The dosage of silica has three variables: (1) the amount of dust; (2) the amount of silica content; and (3) the length of time of exposure. These variants are of the utmost importance, as it can be seen that a small amount of dust inhaled for a considerable period of time is just as dangerous as a great deal of dust containing silica in a shorter time. It is possible, by various methods, to count the dust particles in and around the particular workmen, and chemical and physical analysis will show how much of this dust is silica or silicates or other silica contents. Dust particles under 10 microns may be considered hazardous.

One must consider in the history whether a man works where the sand is dry or wet, and whether a particular person wore a mask and whether the mask formed an effective barrier to the inhalation of dust.

The relationship of silicosis and tuberculosis has received attention by numerous authors, particularly by A. E. Russell,<sup>5</sup> and is discussed fully in Public Health Bulletin No. 187 of the United States Public Health Service. Statistics have

shown definite increase of tuberculosis in those afflicted with silicosis.

Workers who have tuberculosis, even if latent, may develop silicosis more rapidly than those who are not so involved. This is particularly important where there are many negro workers, as they succumb to tuberculosis and silicosis more quickly than the white population. In considering the etiology it must always be remembered that exposure to silica or even the evidence of silicotic deposit in the lungs does not in itself constitute incapacity.

**Symptoms.**—Symptoms due to silicosis itself are, first, gradual weakness, shortness of breath, which increases slowly but surely with the increase of involvement of the lungs. In the first stage the individual may work quite well and it is only after slight exertion that shortness of breath is noticed. An unproductive cough, frequent colds, and chest pains are usually associated with the early symptoms. But a history of exposure, especially under conditions favorable to silicosis, would lead one to suspect even the faintest thickening of the lung markings in an x-ray film as evidence of the beginning of silicosis. As the disease progresses, the symptoms increase considerably, until shortness of breath is constant more or less all the time. A dry hacking cough appears, and is increased by the slightest exertion. Slight blood-streaked sputum is not unusual. Capacity for work is diminished, loss of strength is noted, but usually work may be continued. As a result of the dyspnea, the symptoms usually associated by some with lack of proper oxygenization manifest themselves, particularly those of slight dizziness, headache, loss of appetite, restlessness, etc.

Hemoptysis appears occasionally, especially in patients who cough. The sputum otherwise is clear and has a bluish tinge, is very viscid and is tenacious. Frank hemoptysis is rare.

In the advanced stage one finds an exaggeration of all these symptoms, shortness of breath being the most important and distressing. Later intestinal symptoms are quite common.

Strange to say, many workers even with advanced disease show little or no loss of weight and may have the appearance of robust individuals. Since occasionally symptoms develop years after exposure, a history of previous employment must be obtained.

Death, when it comes, is rarely due to silicosis itself, but must be attributed to associated tuberculosis, secondary abscess of the lung, bronchiectasis, and cardiac disturbances, tuberculosis being the most important cause of death.

**Physical Signs.**—The physical signs vary with the amount of involvement. Because of emphysema and a lack of deep breathing, fine changes in sounds are not often obtained until the disease has progressed either to the second or third stage. At this time the signs are often those associated with tuberculosis rather than silicosis. Cavities due to silicosis alone are rarely discovered on physical examination, first, because they are rare, and secondly, because emphysematous lung tissue is usually present around the diseased areas.

Sayers<sup>6</sup> states, "A certain lack of elasticity of the chest wall" exists during the movement of respiration, together with a somewhat reduced air entry, and a characteristic alteration of the inspiratory murmur from the normal "vesicular" character to a higher pitched to "harshened," "thinned," and commonly somewhat shortened type, the expiratory murmur, although somewhat prolonged, remaining fainter than the inspiratory.

This type of breath with some modification is characteristic of silicosis in all its stages, and has also the significant character of more or less complete generalization. It is first noticeable at the anterior, lateral and basal regions.

Usually there are no accompaniments, but a stray rhonchus may be heard here and there.

**Roentgen Examination.**—It is the *x*-ray examination which is by far the most important in the diagnosis of silicosis. But here again we have numerous complicating pictures which may be due to other diseases that produce somewhat similar fibrotic changes in the lungs. The *x*-ray interpretation of silicotic chests has been discussed by many writers but definite

statements as to making positive diagnosis are rarely seen. It is quite evident that the shadows on the film may be produced by several pathological conditions and a careful analysis of all the facts of the particular case will help materially in a correct diagnosis.

According to Pancoast and Pendergrass the ability to interpret roentgenograms of cases of pneumoconiosis properly must be based upon several factors which may be enumerated as follows: "A knowledge of the anatomy of the chest and many of the physiological problems associated with its anatomical constituents; thorough familiarity with normal roentgenographic and fluoroscopic appearances; knowledge of the histology of the lungs, and especially of the lymphatic system; clear perception of the pathology of the condition of pneumoconiosis and of all conditions which may simulate it in roentgenographic appearances; experienced intimacy with the roentgenographic appearances of the condition in question and of those that resemble it, based upon fundamental knowledge of the pathology represented; knowledge of the physical factors involved in the production of the suspected or pneumoconiosis; and the employment of the proper technic to show to full advantage any or all of the abnormalities present."

The description of roentgen ray films is divided as follows:

1. Definitely negative.
2. More fibrosis than usual.
3. Decidedly more fibrosis than usual.
4. First-stage silicosis.
5. Second-stage silicosis.
6. Third-stage silicosis.
7. Silicosis plus tuberculosis.

These various classifications are described in great detail in a report by R. R. Sayers-Meriweather-Lanza.<sup>7</sup> It is quite evident from the classification that the finest changes in the roentgen films must be considered in placing the patient in the proper class. There are striking discrepancies between symptoms and physical signs of pulmonary fibrosis. Often

the symptoms are minimal in spite of great involvement. consequently it has been the custom of those interested in silicosis to consider the diagnosis from a combination of history, physical signs and roentgen ray studies. At times it is so difficult to make a diagnosis that only at autopsy when the lungs are studied chemically and the silica content is found to be above average, can silicosis be positively identified.

The most important x-ray evidence of silicosis is the increase in the bronchial markings, particularly in the bases, with a preference to the right base. As the silica produces an irritation in the lymph channels, which become blocked and thickened due to an inflammatory reaction, the picture will show these structural changes in direct proportion to the amount of involvement, plus secondary complications such as tuberculosis, bronchiectasis and abscess.

McNally<sup>8</sup> states that: (1) the normal lung contains 1.13 mm. of silicon dioxide per gram of dried tissue. (2) A chemical examination of the lungs should be made in every case coming to autopsy, in which there is a history of a dusty occupation.

Case	Ash per cent	SiO <sub>2</sub> per Gm. of dried tissue, mg.	Occupation
44	10.78	8.6	Millstone sharpener
503	17.14	14.0	Stone cutter
327	12.36	2.4	Machinist
429	14.58	3.6	Engineering draftsman
463	19.99	4.3	Coal miner, 25 years
411	8.84	5.0	Stone quarryman, 9 years
300	8.46	25.0	Granite cutter
446	5.59	10.9	Zinc miner

It can readily be seen by this table that the greater the exposure to silica the higher content of silica in the dried lung.

**Pathology.**—Pathological studies on silicotic lungs have been made by Dr. Leroy U. Gardner<sup>9</sup> of Saranac Lake. A summary of his examination made in 8 postmortems states that the surface of all but one lung presented extensive pleural

adhesions. The sections of the organisms disclosed an appearance which varied with the degree of involvement. The earliest changes due to silicosis alone are small pleural and subpleural nodules of gray fibrous tissue in a lung otherwise not remarkable. The tracheobronchial lymph nodes were small but deeply pigmented and exhibited a few small gray scars. In more advanced cases, sections revealed widespread studding of the tissue with gray-black nodules which were only slightly more compact and firm than the surrounding lung. The distribution was quite general, although the apices and outer third of the lung were somewhat less involved. The remaining parenchyma of the lung exhibited an emphysematous enlargement of the air spaces, readily visible to the naked eye. The tracheobronchial lymph nodes were moderately enlarged and presented a well-defined fibrous body surrounding a dense steel-gray center streaked with lighter bands. The silicotic nodules in cases complicated by tuberculosis were much more dense and much more sharply outlined. They were more steel-gray than black in color and a close examination revealed that they were composed of whorls of silky strands, not unlike the appearance of uterine fibroid tumor. Often they were so closely packed together that a whole lobe seemed to be replaced.

The microscopic appearance in pure silicosis shows slight amounts of dust deposited in the pleural septa and adventitial coats of the vascular and bronchial trunks. These deposits are surrounded by a slight amount of cellular connective tissue. In various alveolae are scattered free phagocytes containing dust particles. As the involvement increases, the evidence of cellular tissue diminishes but is replaced with fibrous tissue, frequently hyaline in character. The blood vessels sometimes are obstructed by endarteritis. The tracheobronchial lymph nodes present even more extensive lesions than are found in the lung. The sinuses are, in most places, obliterated by reaction to excessive amounts of dust or healed and calcified tubercles. Around the node is dense fibrous tissue which had caused a dilatation of the afferent lymph vessels.

Gardner<sup>10</sup> described the silicotic nodules as a "discrete mass of hyaline connective tissue generally surrounded by a capsule of young fibroblasts between which are a great number of dust-filled phagocytes. In the center area the nuclei are compressed to thin elongated spindles lying between very thick, heavy bands of collagen."

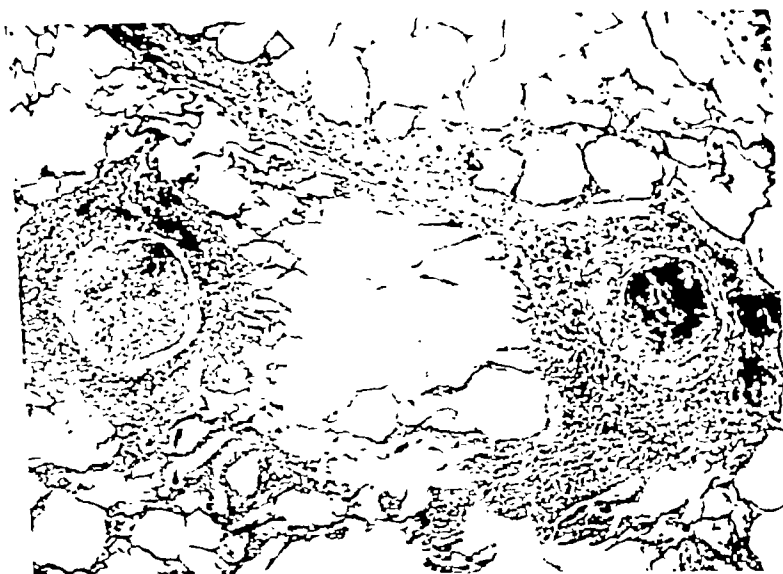


Fig. 37.—Barre granite cutter. Two isolated silicotic nodules. Cellular connective tissue borders and hyaline fibrous centers. Thickened interlobular septum extending upward and to the left of the right nodule. Note dilated lymph vessels in septum. (Taken from "A Pathological Study of Eight Lungs from Employees in the Granite Industry," by Dr. Leroy U. Gardner, Pub. Health Bull. 187, Washington, D. C., 1929, p. 138.)

**Treatment.**—There is no known treatment for silicosis when it is once definitely developed but, at the earliest signs, a change of occupation where the silica hazard does not exist would usually prevent the serious complications. Hemoptysis and dyspnea and pain can be treated symptomatically. The most important contribution to the treatment of silicosis is the prevention.

This has been accomplished by proper safeguards to the



workers by the use of fans, exhaust pumps, filters and inhalators. The change of occupation in plants has been effective.

Compensation to persons afflicted with silicosis has become a legal requirement in most of the states. When compensation is obtained the worker can withdraw from his occupation sooner than otherwise, and thus prevent the later disabling stages of silicosis.

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## CLINIC OF DR. PARK J. WHITE

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### THE CLASSIFICATION AND TREATMENT OF INFANTILE COLIC OR GASTRO-ENTEROSPASM

INFANTILE colic is an excellent example of the difference between "hospital" and "outside" pediatrics. Patients with this condition are not, and should not be, admitted to hospitals.<sup>1</sup> That colic has not lent itself to laboratory study may account in part for the fact that it has escaped the careful classification essential to successful therapy.

**Definition.**—Assuming that such conditions as hunger, improper feeding, otitis media, etc., have been ruled out, we may take as a working basis the definition of the syndrome of "true colic" given in 1923:<sup>2</sup> "Vagogenic gastro-enterospasm, the entire alimentary tract being often involved in the (purely functional) hypermotility. The principal manifestations may include (a) extreme fretfulness, usually aggravated by feeding; (b) projectile vomiting; (c) diarrhea or (more rarely) constipation, with or without visible gastric or intestinal peristalsis." Other terms which have been applied to the condition are "hypertonic infant,"<sup>3</sup> "vagotonia,"<sup>4</sup> and "*gastro-névrose émétisante*."<sup>5</sup>

**Classification.**—The following classification is offered as of practical therapeutic value. The earlier and more accurately one can determine in which of these groups his patient belongs, the earlier he will bring comfort to the sufferer and peace to the parents, to the neighbors, and to himself.

- I Allergic, or sensitive to: (a) Cow's milk.  
(b) Human milk.

(A) *With cutaneous manifestations:*

1. Dermatitis of face or of both face and scalp.
2. Urticaria.

(B) *Without cutaneous manifestations.*

II. Nonallergic.

**Colic in Allergic Infants.**—In 1921, Shannon presented his observations on colic in breast-fed infants as a result of sensitization to foods in the mother's dietary.<sup>6</sup> In the following year he published his paper on eczema in breast-fed infants, relating this disorder to the same etiologic factor.<sup>7</sup> In 1929, I noted that in early infancy, the syndrome of gastroenterospasm associated with eczema is almost three times as common as either condition alone.<sup>1</sup> In that study of 47 infants under three months of age, 27 presented the following sequence of symptoms: colic and diarrhea (simultaneously; less frequently vomiting) at from three to six weeks of age, followed by facial dermatitis at about ten weeks of age. Ten of the 47 had colic alone, and 10 eczema alone. The eczema in those who had it with colic was less severe than in those who had it without colic. Of the 47 patients, 29 were boys and 18 girls—a proportion which holds good for the patients observed since 1929.

In 40 cases studied during the past six years, the incidence of colic without eczema (24 cases, nonallergic) exceeds that of colic with eczema (16 cases, allergic). Accurate figures on the total incidence of both varieties of colic among healthy young infants are of course not available. My impression is that it approximates 1 per cent.

Of the 16 patients with "true allergic colic," 10 were boys, 6 girls.

**Illustrative Cases.**—1. Jarrett S., a well-developed boy whose severe "cramps" and diarrhea began at the age of two weeks, while on an evaporated milk mixture. There was no family history of allergy. The diarrhea improved on a skimmed milk mixture. At the age of ten weeks he developed

a severe eczematoid dermatitis of the face and scalp. Dryco feeding was instituted with excellent results, the rash clearing almost entirely within two weeks, the fretfulness practically disappearing. At the age of three months he weighed 15 pounds; rice and tapioca (in preference to the more likely allergenic wheat) were added to his diet. Now, at the age of six months, there is only a slight tendency to "scaly scalp." His general condition is excellent.

2. Eloise P., many of whose mother's family suffered severely from various forms of allergy. She was first seen at the age of five months. There was a history of "terrible" colic during the first few weeks of life, followed by extremely "bad" eczema of the face, scalp, and legs. Her colic and eczema did not respond to dryco, nor to sobee, nor to cemas (see below). Evaporated goat's milk with alerdex produced prompt and lasting recovery. At the age of ten months, she was able to tolerate boiled cow's milk. The various cereals had to be given in limited amounts. If these amounts were exceeded, both colic and eczema returned.

At the age of twenty months, she developed eczema in the popliteal folds. This yielded to exclusion of wheat from the diet.

3. Morton N., whose case was exactly similar. He did badly until he was given food free from all animal protein (cemas). He was able to tolerate all cereals except those containing wheat.

4. William C., a well-developed, sturdy boy, whose mother's father and brother were both subject to hay fever. He did very well until the age of eighteen days, when he began to "scream all day," and had 8 stools per twenty-four hours. The breast-milk supply was so small that he was weaned and given a formula of skimmed milk and dextrimaltose. This, together with paregoric and bismuth by mouth, reduced the number of his stools.

Ten days later he developed a facial dermatitis and "yelled with colic." He was given the following formula:

Dryco	.. 28 tablespoonfuls
Barley water	30 ounces
Dextrimaltose	4 tablespoonfuls
6 ounces every four hours, 5 feedings.	

Also elixir phenobarbital, 10 to 15 drops before each feeding. Prompt improvement in both dermatitis and colic resulted. Four weeks later, at the age of nine weeks, he was put on an ordinary evaporated milk mixture without return of his trouble.

*An Instance of "Colic" in an Allergic Child of Ten.*—This boy, whose paternal grandmother had had asthma, was first seen at the age of ten. He had had colic and facial eczema in early infancy, and had "always had trouble with his stomach; also from 3 to 5 watery stools per day, and had never so long as he or his mother could remember passed a day without frequent abdominal cramps." His mother had for some time suspected him of sensitivity to chocolate.

Examination revealed nothing abnormal. He was 3 pounds under weight. Chocolate and all milk were completely removed from his diet. Within ten days his improvement was striking. His cramps disappeared. He gained weight. Two years later he was able to eat foods cooked with milk; but if he drank even  $\frac{1}{2}$  ounce of milk, or if he ate any chocolate or foods flavored with it, his abdominal pains promptly returned.

Only the "proof-of-the-pudding" test was done in this case. Skin tests were not considered necessary.

I present the last case to emphasize that, although it is rarely encountered in later childhood, the syndrome of colic due to allergy may occur then and should be watched for.

*Comment on the Treatment of Colic in Allergic Patients.*—Obviously, if sensitivity to food is responsible for the colic and eczema of these infants, milk is the food which we must consider. If, as is seldom the case, the mother has an adequate supply of breast milk, the successive elimination of some of the common allergens from her diet is of course advisable. The babies' symptoms begin several weeks before orange juice and cod liver oil are given. It happens that in

only one of the 16 infants observed during the past six years could breast milk be considered a factor. As the mother gave only from 1 to 1½ ounces per feeding, the baby was weaned in order to eliminate as many "unknowns" as possible. In this case an ordinary cow's milk mixture effected some improvement; but half-skimmed milk dried by the Just-Hatmaker roller process (dryco) was eventually required for complete relief. Inasmuch as the other mothers' milk "dried up" before the babies' fretfulness began, what might well be called suckled nervousness could not be held responsible for the subsequent colic.

These babies were all fed on ordinary evaporated milk, sweet milk, or lactic acid milk mixtures before the syndrome of "true colic" made its appearance. And until the eczematoid dermatitis was noted two or three weeks later, the dietary and medicinal treatments of nonallergic gastro-enterospasm were employed (*q. v.*). Once the allergic nature of the colic was established the indication was either to alter the milk so that it could be tolerated, or to give a substitute for milk which would provide all the necessary food constituents. Dryco produced the most consistently good results, presumably because of the alteration of the lactalbumin by the drying process. Ten of the 16 patients were either cured or greatly improved by its use. From two to ten months' feeding of dryco were required before ordinary milk mixtures could be tolerated. The others required either milk-free soy bean flour mixture (sobee) or the vegetable emulsion entirely free from animal protein, known as cemac.

Acidified milk has continued consistently to aggravate infantile colic. I have seen only one enterospastic do well on it, and his improvement lasted for only one month.

All but one of the allergic group were of the "sthenic type" of body build. The one exception was a girl.

**Colic in Nonallergic Infants.**—Of the 24 patients in this group, 14 were boys and 10 girls. (Thus for both groups, 60 per cent of the patients were boys.) All of these infants were of the "broad or sthenic type" of body build. This accords

with the findings of Haas,<sup>3</sup> who calls such infants "hyper-tonic."

Ten years ago, atropine was the therapeutic mainstay in the treatment of colic. The fact that in prescribing atropine for infants one must warn the parents of the flushing which is very likely to occur, and of the high fever<sup>8</sup> which it less commonly produces, naturally makes one hesitate to use it, and stimulates one's search for reliable dietary means of relief. Hence, in the 24 cases of "nonallergic colic" observed during the past six years, atropine was tried only twice (in severe cases of gastrospasm). In one case there was no benefit, in the other there was a bad reaction.

*Illustrative Cases.*—1. Ronald H., whose family history was negative for allergy, weighed 5 $\frac{3}{4}$  pounds at birth, gained to 16 pounds at four months. When first seen at the age of eight weeks he was on an evaporated milk mixture. He was "very colicky and had a bad diarrhea." He responded very well to the following feeding:

Sweet milk	32 ounces
Farina	5 level tablespoonfuls
Corn syrup	1 tablespoonful
cooked for one and one-half hours in a double boiler to a mushy consistency, divided into 5 equal portions, fed through a Hygeia nipple with the end cut off.	

He became quite constipated, so equivalent amounts of Baby Ralston, later Ralston food were substituted, with resulting normal movements. At the age of ten months he still requires thick cereal.

*Case II.*—Katherine W., whose family history was negative for allergy, began vomiting (projectile) at the very unusually early age of four days. Atropine was given fifteen minutes before each breast feeding, but it was discontinued after 3 doses because each administration produced cyanosis, without checking the vomiting.

On the fifth day, the following feeding was given:

Pumped breast milk plus sweet milk to make 14 ounces.

Farina . . . . . 4 tablespoonfuls

Cane sugar . . . . . 1 tablespoonful

cooked two hours in a double boiler, cooled, divided into 6 "thick feedings," 1 warm feeding every four hours through Hygeia nipple with the end cut off.

The vomiting promptly stopped and the weight curve turned upward. The feedings were of course increased in amount as both appetite and weight increased. Bulgarian milk was given at the age of seven weeks. During the second and third days of this feeding, she began to "shriek," had 10 stools per day, and the projectile vomiting returned. The thick cereal was of course resumed. For ten months, any attempt to change to other food produced the same result. After five months of age, Ralston thick cereal instead of farina was well tolerated, as were also the vegetables purées.

After the age of ten months the "regular second-year diet" produced no untoward effect. Aside from "stomach aches" incidental to teething and to respiratory infections, she has remained free from gastro-intestinal symptoms until the present time (she is now eight years old).

*Comment on the Treatment of Nonallergic Patients with Colic.*—Additional case reports would be both tedious and profitless. In all cases, whether allergic or nonallergic, until the dietary treatment became effective, elixir of phenobarbital was given before each feeding, in dosage of 10 to 30 drops in a half teaspoonful of water. Its carminative and mildly sedative properties make it very helpful as a temporary measure. When vomiting (gastrospasm) predominates, it is best given fifteen to twenty minutes before each feeding.

Until the "colic" has been fully overcome, the act of feeding often starts the peristaltic rushes with resulting cramps—at times even inability to eat. Feeding "colic" patients oftener than every four hours is inexcusable. A few of these infants are satisfied (even at six to ten weeks of age) with only four feedings in twenty-four hours.

Of the 24 cases in the nonallergic group, 8 were relieved



by the substitution of barley water (usually 4 tablespoonfuls of barley flour boiled one-half hour in a pint of water) for plain water cooked with the sweet milk. Thus it would seem that some cases are "mild" enough to respond to "thin cereal," like barley water with milk; and that others are so severe as to require actual thickening of the food, or at any rate a larger amount of the cereal. In 3 of the 16 patients relieved by the "thick cereal," modification of the milk by barley water was tried first, without success.

In 3 of these 24 cases, time was lost because of the mistaken idea that they belonged in the allergic group. In one case dryco was tried, in another sobee, without improvement. They were promptly relieved by thick farina or thick cream of wheat. It should be borne in mind that some infants who might have gone on to develop such a manifestation of allergy as eczematoid dermatitis may have failed to do so because of alteration of the milk protein (probably lactalbumin) by prolonged cooking with the cereal.

**Rationale of Thick Cereal Feeding in Gastrospasm.**—For the past fifteen years, pediatricians have considered thick cereal feeding an important part of the medical, often preoperative, treatment of organic pyloric stenosis. Its beneficial results have been attributed to its consistency, which has been thought to make it mechanically difficult to vomit.

As early as in 1914, the use of thick cereal in the treatment of vomiting was not confined to cases of organic pyloric stenosis. In that year, McClure<sup>9</sup> reported its successful use in a three and one-half months old infant who was evidently a ruminator. He called the condition "neurotic vomiting," apparently because of the "wilfulness of the vomiting." He did not relate it to the autonomic nervous system. Four years later Sauer<sup>10</sup> published his observations, since more widely known, on 6 cases of neurotic vomiting and 12 cases of organic pyloric stenosis.

The administration of cereal to infants under two months of age would have scandalized teachers and practitioners twenty years ago. Yet my patient, Katherine W., at the age

of four days was unable to retain even breast milk until it was cooked and thickened with farina.<sup>11</sup>

It would seem that the consistency of the food is not the only factor in its efficacy in either gastrospasm or enterospasm or both. I cannot help taking seriously Rogatz's statement<sup>12</sup> that "a thick cereal promptly becomes thin and liquid in the stomach, because of (1) saliva and (2) body temperature." He found that mashed potato or vegetable purées underwent less liquefaction in the stomach; and that any thick feeding makes the stomach smaller, more circular in shape, and greatly reduces the size of the air bubble.<sup>13</sup> He considers that this is due to excitation of the peristaltic reflex, with increase in the capacity of the stomach wall to grasp and surround the food.<sup>14</sup> Thus the response of the stomach itself must be considered.

#### **Rationale of Thick Cereal Feeding in Enterospasm.**

—When eczematoid dermatitis, or when careful history alone, indicates the probability of an allergic basis for colic, the mechanism of production of painful peristaltic rushes is not entirely vagogenic, but one of edema and smooth muscle spasm. With regard to treatment, the importance of the point lies in the fact previously noted,<sup>1</sup> that atropine, the vagoplegic, is seldom efficacious in the gastro-enterospasm of allergic infants.

In the nonallergic infants, on the other hand, the mechanism of production of "cramps and rushes" is less clear. Whether the presence of excessive amounts of choline derivatives is a factor is not yet known.<sup>15</sup>

The remarkable results of thick cereal feeding in so many of these cases (in which atropine has either failed or has had to be abandoned because of toxic effects) practically constitute a "therapeutic test." The overemphasis which pediatricians have placed on the mechanical effect of the food's consistency has often been misleading. That such a food could help both the vomiting of gastrospasm and the cramps and diarrhea of enterospasm did not occur to me until Dr. T. C. Hempelmann suggested it in consultation on a patient

ten years ago. I had wanted to use it for the infant's projectile vomiting, but feared to do so because of the diarrhea and because the infant was but a month old. The baby's vomiting and diarrhea both responded to thick farina at once.

**Effect Similar to That of Barium Emulsion.\***—I have long felt that giving an infant (or even an adult) anything as bulky and as nonabsorbable as an emulsion of barium sulphate for roentgenographic purposes would have a soothing effect on excessive and painful contractions of the alimentary tract. Recently I asked Drs. Moore, Larimore, and Zink of our Department of Radiology, also Drs. Ernst and Muench of St. Louis, whether a barium meal could not (temporarily) relieve an infant or adult with intestinal colic. All agreed that they had repeatedly seen such relief occur during and shortly after gastro-intestinal x-ray series. They further agreed that cereal emulsion might well have the same mechanically soothing effect as either barium or bismuth.

If, as has been claimed,<sup>16, 17</sup> strained vegetables and cellulose given to very young infants can increase the bulk of the stool without increasing peristalsis, neither barium nor thick cereal should prove more stimulating. Of course the roentgenographic dose of barium, or of bismuth, so far exceeds the therapeutic dose that for our purposes these considerations are of only academic interest. Bismuth has been used for years in the treatment of intestinal cramps. In infantile colic

\* Since returning proof of this paper, I have read the article, "Infantile Vomiting, Its Relief by x-Ray," by R. A. Higgons, T. West, and M. Duryee, *Jour. Pediatrics*, 9: 81, July, 1936. These authors present records of ten infants with intractable vomiting, one of whom had organic pyloric stenosis. It is their experience that barium alone has no beneficial effect; that relief of vomiting is due to the x-rays (in small dosage). They maintain that x-ray therapy is of value whether the vomiting is due to hypertrophic pyloric stenosis or to "functional pylorospasm." Like Barbour and others, they have noted the beneficial effect of x-rays on the vomiting of pyloric stenosis when the rays have been used in the treatment of thymic enlargement. In my opinion, before definite conclusions can be reached: (1) roentgenologists should be able to explain the mode of action of the x-rays in these cases; (2) more infants should be given x-ray treatment without preliminary administration of barium meals.

it has never given the consistently good results obtained by thick cereal.

**Possible Colloidal-chemical Effect.**—Every one of my 16 nonallergic enterospastics receiving thick cereal had previously done badly on a variety of liquid foods. The mothers of 3 of these infants were quite certain that orange juice and water, the only liquid material ingested, regularly produced "upsets." That the mechanical consistency of the food is mainly responsible for its benefit, there can be little doubt. But often the effect of the cereal feeding, and at times even that of adding barley water to the milk, is so striking as to be considered medicinal. We should concede the significance of Gasser's remark,<sup>18</sup> "We have much to learn about the pharmacology and the colloidal chemistry of foodstuffs and their contained gels."

**Significance of Body Build, Gastric Secretion and Motility.**—Discussing the importance of individual variations in type, Washburn<sup>19</sup> gives a graphic x-ray demonstration of the marked difference in the gastric emptying rates of two normal infants.

Siemsen and Ledoux<sup>20</sup> performed fractional gastric analyses, balloon motility, and radiologic studies on 12 children of various types of body build. They found no definite relation between gastric secretory function, body build, form and position of the stomach. The motility was found to be somewhat greater in the "broad" type.

Let me repeat that all but one of the 40 patients with both types of colic reported herewith were of the "sthenic," or "broad" type, with every evidence of gastric, oftener intestinal, hypermotility and peristaltic rushes. They were thus quite the opposite of the more relaxed, "asthenic" infants, so likely to acquire visceroptosis with the vertical position.<sup>21</sup>

In our noisy gastro-enterospastics, alimentary hypermotility dominates the picture. Their symptoms are almost uniformly aggravated by acid milks. This observation is substantiated by the fact that Schlutz and Fetter<sup>22</sup> found high gastric activity in more than 50 per cent of their cases follow-

ing the ingestion of acidified milks—a much higher motility than was observed with sweet milk, or with evaporated or powdered milks. Such infants may be classified with the 12 cases reported by Sauer, Minsk, and Alexander<sup>23</sup> as having high free acid, rapid emptying time, and good appetite—in complete contrast with the 21 hypo-and-asthenics described by these observers. Feeble premature infants, who *require* acid milks because of their low gastric acidity,<sup>21, 25</sup> belong more properly to the latter group.

**Drugs in the Treatment of Infantile Colic.**—Fortunately, the majority of parents, and a rapidly increasing number of physicians, are opposed to the use of drugs in early infancy. Thus, one is likely to be criticized for giving palliative medicines even while waiting for the dietary treatment to take effect.

*Atropine.*—The methods of administration of this drug have been fully described elsewhere.<sup>2</sup> It is particularly useful in cases of gastrospasm with projectile vomiting. Owing to the likelihood of atropine fever,<sup>8</sup> flushing, dilatation of pupils, etc., one is glad to find himself able to avoid this medication. The malic acid compound of belladonna leaves (bellafolin, Sandoz) is less toxic than atropine, which is a racemic derivative.

*Phenobarbital.*—The relaxing effect of this mild sedative is well-known. When given to infants under three months of age, the elixir should be used, in doses of 10 to 30 drops in  $\frac{1}{2}$  teaspoonful of water, immediately or fifteen minutes before each feeding. Presumably it has also a carminative effect. It is an excellent temporary expedient.

*Camphorated tincture of opium (paregoric)* is justifiable for only a few days (4 to 10 drops in  $\frac{1}{2}$  teaspoonful of water before each feeding) when diarrhea is the principal part of the syndrome.

*Calcium.*—I have never had any reason to suppose that any of my colicky infants was suffering from smooth-muscle tetany. Hence I have not used calcium except occasionally as the caseinate (casec) in bad cases of diarrhea.

*Alkalis.*—Sodium bicarbonate, sodium citrate ("citrated milk") were formerly used much more than they are today. If acid milks aggravate the various forms of colic, one should of course expect alkali therapy to be beneficial. As a matter of fact, the higher buffer content of sweet cow's milk obviates the necessity of adding alkali; and as far as the starchy cereal is concerned, this is digested by the intestinal juices, which are sufficiently alkaline.

**Conclusions.**—1. Proper classification of infants with colic or gastro-enterospasm is an important preliminary to proper therapy.

2. Allergic infants, with gastro-enterospasm and eczematoid dermatitis, require alteration of the milk protein by heating or drying, or else some dietetically adequate substitute for milk.

3. Nonallergic infants with gastro-enterospasm can practically always be relieved by thoroughly cooked thick cereal-milk feeding. About one fourth of these cases can be relieved by feeding barley water cooked with the milk.

4. In these functional cases, peristaltic rushes, with intermittent spasmodic contractions of the intestine, make diarrhea commoner than vomiting.

5. Of 16 allergic and 24 nonallergic infants with gastro-enterospasm, all but 1 were of the "sthenic" or "broad" type. Twenty-four were boys.

6. Thick cereal cooked with milk, and even strained vegetables, are very well borne by infants less than three months of age. Peristalsis is not necessarily increased by them, although the stools are larger.

7. The quieting effect of thick cereal is probably due to (a) mechanical action of the bulky, bland food, similar to that of large amounts of bismuth or barium salts, and (b) to colloidal-chemical action of the food gels.

8. Increasing knowledge of both classification and dietary treatment of gastro-enterospasm of early infancy is rendering drugs less important in its therapy. Elixir of phenobarbital is the best temporary expedient.

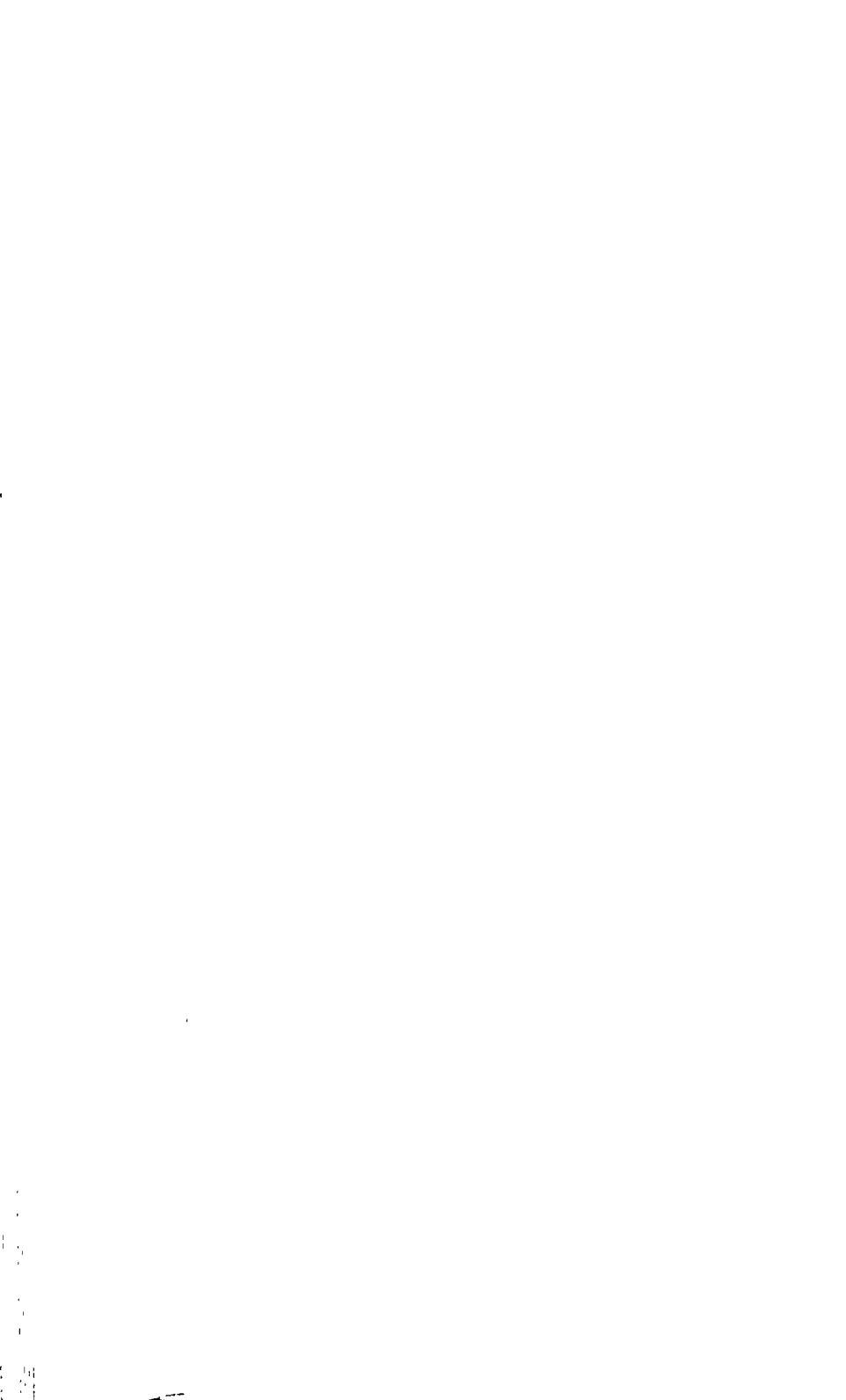
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### THE TREATMENT OF UREMIA

THE physician faced with the problem of treating a case of uremia realizes that he is handling a difficult problem with little hope of permanently satisfactory results. The prognosis is grave, and there is seldom hope for ultimate recovery. These patients, however, are often exceedingly uncomfortable, and proper treatment may afford considerable relief in their few remaining days.

Although the term "uremia" includes any disease accompanied by nitrogen retention, the most common etiological factor is kidney insufficiency, and this discussion will be confined to the treatment of uremia due to chronic nephritis, whether it be vascular or renal in origin.

The treatment of uremia should include dietetic, diuretic, as well as symptomatic or supportive measures. It must be remembered that the patient should be treated as a whole and attention not confined to the azotemia while other needs are neglected.

The diet must be nutritious and palatable. Dietary principles should be followed but too rigid restriction of certain constituents may make a diet so distasteful that the patient refuses to consume enough food to meet his basal requirements. Since the uremic patient is seldom very active, a daily intake of 2500 calories is usually sufficient. The greater portion should be derived from the more easily digestible car-

bohydrates such as fruit, fruit juices, vegetables, cereal gruels, sugared desserts, toasted bread, jams and preserves. Carbohydrates should predominate since many uremic patients have difficulty in the digestion of fats and since nausea may be increased by a high fat diet.

Although in chronic cases the protein intake should be moderately restricted, too rigid limitation tends to increase the anemia and cardiac weakness. Formerly, diets containing 25 Gm. or less of protein were often advised. When, however, the protein is so rigidly restricted over a long period, nitrogen equilibrium is not maintained and body protein is consumed. In an acute exacerbation of chronic uremia or in uremia complicating acute nephritis, a protein intake of less than 40 Gm. may be advisable for a few days only. After this interval the protein in an adult's diet should be gradually increased to a daily intake of 50 or 60 Gm.

Frequent determinations of the blood urea or nonprotein nitrogen are often of considerable assistance in determining the optimum level for protein intake and it may be found that a diet containing 60 Gm. a day will have no greater tendency to increase nitrogen retention than would one containing 25 Gm. Ordinarily it is wise to reduce the protein content of the food when nitrogen is rapidly accumulating in the blood.

Protein may take the form of milk, egg, meat and fish. The statement that the "red" meats are harmful and should be avoided has never been established. A small portion of broiled steak is often more palatable and does not produce any more tendency to nitrogen retention than would an equal amount of fish or chicken breast.

It is important to give the patient's family specific instructions regarding the diet. The mere statement that certain foods should be forced and others restricted is not sufficient. O'Hare<sup>1</sup> has devised a practical chart which enables the patient or his family to determine his food allowance within a short time. O'Hare informs the patient that he may have a certain number of points daily. Each point on the chart represents 4 Gm. of protein. There is also included

a list of unrestricted foods high in carbohydrate of which the patient is urged to partake freely.

The writer has found the following diet, which was originated by the dietary service of the Peter Bent Brigham Hospital, useful in cases of chronic uremia. It contains approximately 60 Gm. of protein and sufficient calories for the average patient. The nutrition is usually maintained and often there is no increase in nitrogen retention for a considerable period. The diet is simple, the constituents are interchangeable and easily prepared.

<i>Food</i>	<i>Gm.</i>	<i>Household Measure</i>
<i>Food Morning</i>		
Grapefruit or orange	100	$\frac{1}{2}$ ,
Oatmeal . . . . .	60	2 tablespoonfuls
Egg . . . . .		1
Toast . . . . .	30	1 slice
Butter . . . . .	5	1 square
Cream (40 per cent)	80	$\frac{1}{8}$ cup
Milk . . . . .	240	1 cup
Jam . . . . .	30	2 tablespoonfuls
<i>Food Noon</i>		
Roast mutton, steak or chicken	60	1 small serving (2 ounces)
Baked potato . . . . .	90	1 medium
Peas with . . . . .	50	2 tablespoonfuls
Butter or . . . . .	5	1 square
Onions with . . . . .	150	1 saucer
Butter . . . . .	5	1 square
Bread . . . . .	30	1 slice
Butter . . . . .	5	1 square
Bavarian cream . . . . .		1
Fudge . . . . .	35	2 squares
<i>Food Night</i>		
Lettuce or . . . . .		2 leaves
Tomatoes, fresh . . . . .	120	1 tomato
Celery hearts . . . . .	35	1 serving
String beans with . . . . .	150	1 saucer
Butter or . . . . .	5	1 square
Asparagus with . . . . .	150	1 saucer
Butter . . . . .	5	1 square
Bread . . . . .	30	1 slice
Butter . . . . .	5	1 square
Pears . . . . .	100	2

The total daily intake of sodium chloride must depend upon the condition of the patient. In the presence of edema and a normal blood chloride salt should be restricted. Many believe that it should be limited to 2 Gm. or less per day. Fishberg<sup>2</sup> advocates a restriction because of diminution of the ability of the kidneys to excrete salt. In those cases of vomiting followed by hypochloremia, however, he believes that the dietary salt should be increased. Even in the absence of vomiting the blood chloride may in the late stages be low and some patients seem to improve with a salt intake increased to as much as 10 Gm. Because of nausea it may be necessary to administer this by subcutaneous or intravenous routes.

An attempt should be made to increase the amount of urine. The uremic patient excretes urine of a low and fixed specific gravity. Large amounts are required to remove the excretory products normally present in a much smaller urinary volume. Often every attempt to increase the output is met with failure, which in certain cases may depend upon the extent of destruction of the secretory apparatus of the kidney.

Diuretics are seldom of value and must be used cautiously. The most powerful, salyrgan, novasural, mercupurin, may be retained and produce severe mercurial intoxication. The writer has seen diuresis and temporary improvement in a few cases in which salyrgan had been used in conjunction with intravenous fluids. Theobromine and theophylline derivatives may be used but seldom increase the urinary output.

Probably the most effective diuretic in uremia is glucose given intravenously. This is usually administered as a 10 per cent solution and may be given in saline or distilled water. As early as 1894 Beverly Robinson<sup>3</sup> advised the use of sodium chloride rectally. Keith<sup>4</sup> warns that the daily injection of sodium chloride intravenously may cause oliguria. He reported two cases of oliguria following intravenous administration of 10 per cent glucose in 1 per cent saline. Diuresis occurred when the glucose was given without the sodium chloride. Bannick<sup>5</sup> advised the use of glucose in saline and

suggests 1000 cc. to be given over a forty-five-minute period. He observed no increase in oliguria. Others believe that hypertonic solutions of glucose (20 to 50 per cent) are more effective in producing diuresis but this has not been the experience of the writer.

In the absence of vomiting, adequate amounts of fluid should be administered orally. This may be in the form of water or fruit juices. Often the carbohydrate intake may be increased by adding lactose to fruit juice with the double purpose of increasing carbohydrate and fluid consumption.

In forcing fluids one must always remember that the patient may have a weakened myocardium. Many uremics have had for years hypertension with resultant cardiac damage. The fact that the kidneys are decompensated should not allow one to forget that the cardiovascular system is probably functioning far below its normal efficiency and it is possible that some cases of pulmonary edema have resulted from the injudicious forcing of fluids. It is seldom advisable to exceed a daily fluid intake of 3000 cc. in the uremic patient.

Often bed rest and digitalization will increase the urinary output by improving cardiac efficiency. There is no evidence to show that the tolerance for digitalis differs in the uremic patient. Vomiting may make it difficult to administer orally and intravenous or intramuscular routes may be necessary. Thevetin may be given intravenously in an attempt to improve and maintain cardiac efficiency. The writer recently observed an increase in the urinary output in a case of uremia following thevetin administration in which digitalis had apparently failed. Fantus<sup>6</sup> advised the administration of strophanthin in these cases. The use of digitalis in uremia could hardly be considered as an emergency measure and need not be given too rapidly. Miraculous improvement could not be expected in the patient in deep coma. Six cat units daily may be administered until evidence of digitalization appears. This should be followed with a maintenance dose of 1 to 2 cat units daily.

Frequently attempts are made to increase extrarenal ex-

cretion. The bowels should be kept open and moderately loose. Profuse diarrhea should be avoided because of its weakening effect upon the patient. The constipated individual may be given magnesium or sodium sulphate in moderate doses. A large dosage of the saline cathartics usually does not produce diarrhea in a uremic patient, while the same dose might cause a marked upset in the normal individual. Recent work<sup>7</sup> indicates that some caution should be used in the administration of magnesium salts in renal insufficiency. A condition simulating uremia may appear as a result of excessive magnesium administration. One seldom encounters difficulty, however, and frequently sees some improvement when 16 to 30 Gm. of magnesium sulphate are given daily to the uremic patient.

Although sweating is a procedure that has long been popular in the treatment, the amount of nitrogenous material removed by perspiration is insignificant. The procedure is often weakening and its too enthusiastic use has been responsible for collapse. If this measure is to be used it should be done cautiously. Moderately warm baths of thirty minutes' duration followed by wrapping in warm blankets may create a sense of well-being and avoid the collapse following the more drastic procedures.

The patient having convulsive seizures must be handled carefully but treatment should not be delayed. There remains some difference of opinion regarding the etiological factors producing the convulsions. Some contend that cerebral edema produces the episodes while others believe that cerebral anemia is the most frequent cause. In younger individuals cerebral edema is more frequently found. This should be combated by hypertonic fluids. In the face of impending convulsions 50 per cent magnesium sulphate (90 to 180 cc.) may be administered rectally with every attempt made to avoid immediate expulsion. With coma fluids should be given intravenously.

Pollitzer<sup>8</sup> advised the use of 10 cc. of 10 per cent magnesium sulphate twice daily in children and believes that the

mental condition is improved as a result. Aldrich<sup>9</sup> uses 100 to 200 cc. of 2 per cent solution intravenously. Fishberg<sup>2</sup> suggests the administration of 15 cc. of 20 per cent magnesium sulphate intramuscularly in adults. Hypertonic glucose may be given in amounts of 25 to 50 cc. of 50 per cent solution or 100 to 200 cc. of 20 per cent solution.

Venesection often stops convulsions and may control stupor and coma. Approximately 200 to 300 cc. should be removed quickly. In the presence of severe anemia it is wise to follow the phlebotomy with a transfusion of 300 to 400 cc. Bannick<sup>5</sup> has found that transfusions lessen the anemia and decrease the tendency to epistaxis, which is often a troublesome symptom.

Sedation may be necessary to combat restlessness, headache, and insomnia. The use of opiates should be avoided until other measures have failed. Chloral hydrate or paraldehyde occasionally afford some rest. Sodium phenobarbital subcutaneously has been administered successfully in some cases. It should always be remembered that renal excretion is poor and drug intoxication may occur. Lumbar puncture has relieved the headache and restlessness and reduced the tendency to convulsions in some patients.

After other measures have failed to combat restlessness and delirium it may be necessary to resort to morphine. This should be used cautiously, however, and the respirations should be carefully observed. Small doses are indicated. The writer recently observed one uremic patient develop very alarming Cheyne-Stokes respiration after 0.01 Gm. of morphine. The patient improved after carbon dioxide inhalations and caffeine intravenously. A similar episode occurred several days later when morphine was again administered for severe restlessness. This patient lived several weeks after these two episodes and exhibited Cheyne-Stokes respiration at no other time. Fantus<sup>6</sup> advises the use of morphine to combat hiccup, dyspnea, cramps, and restlessness.

Pruritus is often very annoying and is usually extremely difficult to control. Fishberg<sup>2</sup> advises the intravenous injec-



tion of sodium bromide but states that an eruption may occur. O'Hare<sup>10</sup> believes that nothing is as effective as sponging with vinegar or weak acetic acid. Lichtman<sup>11</sup> and others have used ergotamine tartrate with success. The writer has recently observed a uremic patient who had considerable relief from pruritus after administration of 1 mg. of ergotamine every night. The possible danger<sup>12</sup> of this drug to the vascular system in a patient with poor renal function must be considered.

Vomiting is often difficult to control. Gastric lavage with 10 per cent sodium bicarbonate solution followed by duodenal tube administration of 1 to 2 liters of warm water or normal saline may prove helpful in some cases. Fishberg<sup>2</sup> has had some success with cocaine in doses of 0.013 Gm. by mouth. The nauseated patient occasionally is afforded relief by small amounts of ginger ale or carbonated water.

#### SUMMARY

In treating a patient in uremia, the physician must remember that the prognosis is grave with practically no hope for ultimate recovery. All measures are palliative and therapeutic attempts should be directed toward maintaining the patient's nutrition and keeping him as comfortable and cheerful as possible. The therapy advised above consisting of dietetic, diuretic and supportive measures has been directed toward those purposes. Every patient must be regarded as an individual problem and treated as such. Any safe procedure relieving the distressing symptoms and providing comfort and peace to the uremic patient deserves consideration and commendation.

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## CLINIC OF DR. DREW LUTEN

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### THE SIGNIFICANCE OF ABNORMAL CARDIAC RHYTHMS

DURING recent years clinical conceptions of the significance of abnormal cardiac rhythms have undergone great changes in many particulars. The development of graphic methods of registration of the heart beat twenty-five or thirty years ago led to better understanding of the various abnormalities of rhythm, and thus facilitated clinical differentiation. New interest in the arrhythmias tended to focus attention on them, and to assign them a clinical significance now regarded as being out of proportion to their true importance. Certain abnormal rhythms were regarded as entailing particularly harmful consequences upon the heart muscle, and as being themselves the cause of any attendant cardiac embarrassment. For many years the chief interest of physicians in such cases generally lay in the employment of measures designed primarily to influence the disordered beating, with the object of restoring the myocardium to more normal status by such means. Consideration of factors concerned in the production of the various arrhythmias was secondary to the matter of the treatment of them.

Information regarding certain causes began to accumulate, however, and it was soon recognized that in some instances neither the circumstance of origin nor the consequences of abnormal beating were such as to necessitate special treatment.

In certain cases treatment began to be directed primarily to the abnormal situation producing the arrhythmia rather than to the disordered beating itself.

In more recent years this interest in the origin of the arrhythmias has increased. Consideration is given to the matter of cause as well as to question of effects. At present there is a growing tendency to consider abnormal beating of the heart in connection with other abnormalities observed in the patient; to view it in relation not to the heart alone, but to the various factors concerned in the heart beat. Attention is given not only to the heart muscle but to toxic and nervous influences, direct and indirect, which are known to influence the initiation and propagation of contraction. Extracardiac factors are considered.

Whatever ultimate factors may be concerned in abnormal beating, however, it is obvious that the immediate causes in a particular case must be referred to that part of the heart in which the arrhythmia arises. It is not within the province of this discussion to attempt any analysis of the precise physiologic processes of nerve and muscle responsible for the origin and propagation of impulses in the heart. Many aspects of this complex problem are unsolved. It is well known, however, that both muscle and nerve factors are concerned, and that in proportionate importance both are subject to great variation. In certain instances either the nervous or the muscle elements may predominate; upon occasion one or the other may be negligible. The nervous factor, moreover, may be applied ultimately through reflex channels, no cardiac lesion being involved.

In assessing the significance of an abnormal cardiac rhythm in any case, it thus becomes apparent that interest attaches not only to the question of the integrity of the heart but to possible extracardiac influences as well. Either may be the sole causative factor, both may be involved. Abnormal beating of the heart thus may be a diagnostic sign of great importance. Its presence may indicate disease in the heart demanding treatment, or disorder in some other part of the

body calling for primary attention. In both classes of cases, however, consideration must be given also to the following questions: (a) does the arrhythmia *per se* interfere with the functional efficiency of the heart, and if so, to what extent? (b) If functional efficiency is impaired, what therapeutic measures, if any, may be employed directly to obviate the harmful effects of the abnormal rhythm, in addition to appropriate measures directed toward combating the disorder causing the arrhythmia? In other words, does the arrhythmia itself require special treatment irrespective of the condition which produces it?

In the cases of some abnormal rhythms, cardiac efficiency may suffer great temporary embarrassment even though little permanent damage accrue to the heart. The general circulation is impaired. In other instances, neither cardiac nor general circulatory effects are in evidence. Certain disordered rhythms frequently arise as a result of some condition which itself is associated with cardiac insufficiency, and it is largely due to this circumstance that the harmful effects of arrhythmias in general have been exaggerated. More commonly in such cases the abnormal condition producing the arrhythmia is responsible for a much greater degree of cardiac embarrassment than the abnormal rhythm itself produces. While in some instances, therefore, therapeutic measures may appropriately be directed toward combating the ill effects of abnormal beating, it is much more frequently the case that the arrhythmia *per se* demands no special treatment, therapy being directed simply to the underlying disease. In most cases the treatment of a patient with an abnormal rhythm is identical with the treatment that patient should receive were his heart beating normally. As with fever, chills, leukocytosis, and other manifestations of abnormal situations, cardiac irregularity may be the sign which points the way to correct diagnosis, and consequently to appropriate therapy; but it is not to the sign that therapeutic measures are directed. As with other signs and symptoms, there are certain exceptions to the general rule that irregular heart action calls for no special

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treatment. They will be noted in the following brief consideration of the several abnormal rhythms.

**Sinus Arrhythmia.**—The mechanism for reflex change in heart rate is delicately adjusted so as to respond readily to various influences. Demonstrable variation in sinus rate is common in healthy subjects at rest, representing an exaggeration of normal physiologic processes. Sinus arrhythmia of nervous origin frequently occurs in response to causes which have little effect upon the heart other than the variation in rate, the vast majority of instances falling into this category. Pathologic processes of the auricle also may be responsible, minor as well as serious lesions. It is not unusual for high-grade sinus arrhythmia to be noted in certain cases of coronary thrombosis. That it may result from the administration of digitalis is well recognized.

This irregularity, the simplest as well as the commonest of the arrhythmias, exemplifies the general principles stated above; viz., that irregular heart action is a sign which calls for examination, that it may result from causes of various degrees of seriousness, and that in general it requires for itself no special therapy, treatment of the patient being directed to the condition which produces it.

**Extrasystoles.**—While it is true that the organized tissues of the heart under certain circumstances are able to initiate spontaneous contractions under the usual normal conditions of activity when exercised. In the strictest sense, they should be regarded as pathologic, but they are usually separate the nervous and muscular elaboration of spontaneous beats. The particular situation responsible is usually cardiac or extracardiac. Wherever it appears in many instances to represent an exaggeration of physiologic processes rather than a true pathologic condition in the usual sense. Premature contractions may be produced experimentally through electrical stimulation,<sup>9</sup> and many instances of clinical



pear to rest upon this basis. Other reflex pathways also may be involved, extrasystoles of emotional origin<sup>4</sup> being well recognized.

On the other hand, the ultimate cause may lay in the heart muscle, where it may represent a negligible lesion or one of extremely serious import. In the cases of patients predisposed to extrasystoles, slight change in the status of muscle or nerves may be sufficient to evoke them. A deep breath may suffice. Toxemia, mild or severe, fatigue, loss of sleep, or any situation which lowers the general level of bodily well-being may produce these interruptions to regular heart action. While it is impossible in any case to determine the precise degree of nerve or of muscle influence in the occurrence of an extrasystole, it is quite frequently possible to refer them chiefly to nervous or to myocardial origin. In general, premature contractions arising in the auricle are more likely to result from nervous influences, those of ventricular origin to be due to muscular factors.

Extrasystoles call not only for examination of the heart, but for complete examination of the patient. In many cases, no cause is found. Therapy appropriate to the etiologic factor, if discovered, should be instituted, but usually the arrhythmia itself demands no treatment. In some cases, however, the patient is so annoyed or perturbed by the irregularity that special measures should be employed to mitigate it. Strychnine frequently is effective. The more rapidly eliminated barbiturates may be useful. On the other hand, there is experimental evidence that barbiturates may cause extrasystoles. Digitalis is a frequent cause, while upon occasion the drug may abolish the arrhythmia.

**Auricular Fibrillation; Auricular Flutter.**—These arrhythmias are so nearly related that they will be considered together. In origin they are closely akin to auricular extrasystoles. In general what has just been said with regard to auricular premature beats applies also to auricular fibrillation and flutter. Although most cases occur in patients with heart disease, it is now recognized that these arrhythmias may occur

in the auricle of a heart which gives no evidence of any abnormality of the ventricular muscle, and no sign of impaired function.<sup>1, 2, 5, 8</sup> They are auricular phenomena, and it is to the auricle that their etiology must immediately be referred. This discussion will be confined particularly to fibrillation, but in substance it is equally applicable to flutter.

The general principles which link auricular fibrillation (and flutter) with auricular extrasystoles in etiology and in clinical significance, are subject to certain special considerations. As with extrasystoles, the proportionate influence of nervous and (auricular) muscle factors is subject to great variation, auricular fibrillation of purely nervous origin being well recognized.<sup>1, 2</sup> The probability of definite auricular lesion, however, is much greater in fibrillation than in extrasystoles. The proportion of cases with (ventricular) myocardial disease also is conspicuously larger. This special association of fibrillation with clinical heart disease rests upon the following explanation. While nervous factors alone may suffice, in general the initiation of fibrillation requires greater insult to the auricular wall, or at all events is greatly facilitated by it. Auricular lesions obviously are much commoner in the cases of patients with more extensive heart disease. Such lesions as mural thrombi, scarring, and fibrosis are noted in many reports of cases which come to autopsy in which examination has been directed to the auricle. The changes attendant on older age<sup>6</sup> appear to be important factors, auricular fibrillation occurring particularly in older patients. It is relatively infrequent in the heart disease of children, although in such cases another factor which appears to be of great importance in precipitating the arrhythmia commonly is present, *i. e.*, stretching of the auricular wall.<sup>5, 7</sup> The vast majority of instances of established auricular fibrillation are observed in older subjects in cases of congestive heart failure, and in cases of mitral disease with or without congestive failure. In both situations the increase in intra-auricular pressure tends to induce stretching of the auricular musculature. That increase in pressure within the auricle as an

important element in the disorder is indicated also upon experimental evidence.

The etiology of auricular fibrillation may briefly be summarized: it may arise from nervous or muscular factors in varying relationship. The commonest precipitating cause is the increased pressure of congestive heart failure applied to the wall of an auricle in which certain pathologic processes have occurred.

Quinidine abolishes the abnormal rhythm in many instances. If the basic causes are persistent and of great force, however, the arrhythmia usually does not yield permanently to quinidine. Particularly in cases unassociated with serious heart disease or with congestive failure, the drug may restore normal cardiac rhythm and thus free the patient of the annoyance and of any other ill effects of the disorder.

Auricular fibrillation may occur as an incident in the course of many abnormal situations.<sup>3, 10</sup> Quinidine or other measures to abolish it may properly be employed in occasional cases in which the arrhythmia itself is of more consequence than a relatively unimportant cause, or in cases in which the cause is obscure. In any case, however, it calls first for examination. Search should be made for other evidences of congestive heart failure, of which fibrillation is frequently a sign.<sup>7</sup> Thyroid disease and other toxic factors must be considered. Nervous influences are to be kept in mind. The arrhythmia may be an important sign leading to correct diagnosis, and to appropriate therapy. In most instances some degree of heart failure is observed, and in such cases obviously digitalis is to be employed. In cases of other etiology it is equally obvious that other therapy is indicated. It is as erroneous to administer digitalis in cases of auricular fibrillation unassociated with heart failure as it is to omit the drug in instances in which heart failure is the cause. Digitalis does not slow the ventricular rate in nonheart-failure cases,<sup>5, 6</sup> and in such cases of toxic etiology the drug may be disadvantageous. Auricular fibrillation is no more a general indication

for digitalis than is dyspnea or edema. It is to the underlying situation that treatment regularly must be directed.

**Auriculoventricular Block.**—Although in occasional instances vagus influence is known to be responsible, the various grades of auriculoventricular block in most cases result wholly or in most part from lesions of some portion of the ventricular muscle. Heart block generally is a sign of myocardial disease. Upon occasion a lesion apparently confined to the auriculoventricular bundle is responsible, but usually disease processes are not so closely restricted, grave myocardial involvement being inferred in most cases.

Adjustment in blood pressure usually compensates for the slow rate of complete block, the ultimate prognosis being determined largely by the character and extent of the myocardial involvement. Therapy is to be directed to the basic disease in question. Special treatment of the block usually is not indicated, but in cases with Adams-Stokes attacks measures designed specifically to prevent recurrence should be tried.

**Paroxysmal Tachycardia.**—Auricular fibrillation and flutter not infrequently occur in paroxysms, the etiologic agents being either of limited duration or of lesser degrees of potency. Such paroxysmal attacks thus may constitute particularly valuable signs in early diagnosis. As a rule quinidine is employed more appropriately in such cases than in established fibrillation.

Other paroxysmal tachycardias are to be differentiated. Those of supraventricular origin commonly occur in the cases of patients without important heart disease, due chiefly to toxic or nervous influences. Change of position is a frequent precipitating cause. Usually they carry no very great implication of serious import, yielding to milder sedatives and to the reassurance which may truthfully be given. Such a simple procedure as pressure over the carotid sinus may suffice to end the paroxysm.

Ventricular tachycardia, on the other hand, generally occurs only in the presence of serious myocardial insult. It is a sign, therefore, of considerable gravity. It is not uncommon

for an independent ventricular rhythm to result from serious digitalis intoxication or from myocardial infarction. The abnormal sequence of contraction of the ventricular muscle parts renders systole less effective in expelling blood. Serious impairment of the circulation may result and render it advisable to employ measures designed primarily to abolish the abnormal rhythm. In most instances the attack subsides spontaneously before occasion for specific treatment arises. In the average case, therefore, there may be less danger<sup>3</sup> in the employment only of general measures than in precipitate special therapy.

**Alternation.**—Except for brief occurrence, variation in the force of alternate ventricular contractions occurs only in the presence of grave myocardial embarrassment. Continual alternation is of serious import. It is not a disease entity, but an evidence of serious impairment of myocardial function. Its correction rests only upon measures that restore the myocardium to more normal status.

It will be observed that alternation, perhaps the gravest of continued arrhythmias, in common with sinus arrhythmia, the simplest of them, illustrates the principles generally applicable to all; it is a sign, not a disease. Consideration must be given to the cause, rather than to the sign; treatment must be directed to the heart, rather than to the heart beat.

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## CLINIC OF DR. ARTHUR E. STRAUSS

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### TREATMENT OF MYOCARDIAL INSUFFICIENCY

THE treatment of myocardial insufficiency, like that of any other condition, depends upon the accuracy of the diagnosis and a proper interpretation of the significance of that diagnosis together with an analysis of the indications for treatment and of the methods available. It is not our intention to discuss the diagnosis of myocardial insufficiency but mention must be made of the fact that myocardial insufficiency may be of several grades, the treatment of which will naturally differ if not in kind, at least in degree. In discussing this phase it will be well to use the Functional Classification of Heart Disease of the American Heart Association. This classification divides patients with organic heart disease into three groups as follows:

*Class I*—Patients with organic disease, but able to carry on ordinary physical activity.

*Class II*—Patients with organic disease, but unable to carry on ordinary physical activity (without discomfort).

(A) Activity slightly limited.

(B) Activity greatly limited.

*Class III*—Patients with organic disease, but unable to carry on any physical activity, *i. e.*, who must remain in bed or in a chair.

Patients in Class I are included in this consideration of treatment of myocardial insufficiency, though there may be

some who object to their inclusion, because we believe that it is this group that should be considered as having *potential* myocardial insufficiency and thus a proper group for prophylactic treatment. Digitalis and other cardiac drugs usually are not indicated at this stage of the disease, though advocated by some as a prophylactic measure. It is this group of patients who should be taught the value of moderation, the proper relationship of activity and rest (not invalidism), the importance of avoidance of infections, etc. It is also with this group that so much can be accomplished by proper appreciation and treatment of the etiological agent, especially if it be active, such as syphilis or thyrotoxicosis. Let us pause here long enough to emphasize that no treatment of myocardial insufficiency is adequate unless consideration is given to the etiology. Some of the recent advances in cardiology are due to the emphasis placed upon the proper and complete classification of heart disease which has led not only to better diagnosis and understanding of the problems but in turn has resulted in better treatment. Our task would be poorly done if we treated a case of thyroid heart disease with decompensation with rest and digitalis (or quinidine) and neglected care of the abnormal thyroid state underlying it.

We would be overlooking an important element if we failed to recognize an adherent mediastinopericarditis as the factor in certain cases of decompensation and did not consider surgery as an adjunct treatment. Similarly when syphilis is the cause of heart disease, we must give due consideration to antiluetic treatment.

We shall not consider the treatment of acute myocardial insufficiency except to mention that here again treatment of the underlying and causative agent is important.

We shall now consider the treatment of patients who belong in Class II and III, those with varying degrees of myocardial insufficiency, from the mild to the severe.

As soon as we think of treatment in heart disease our minds immediately frame the picture of our chief defenses—digitalis and rest. Truly, these have been and remain our

chief weapons but a battle is not always won by using only the staunchest strongholds or the largest guns, so we must frequently fortify the action of digitalis with diuretics and procure rest with sedatives, hypnotics and opiates. Treatment of heart disease, however, is not quite so simple. As in warfare we adapt our attack to the character of the enemy, his number and aggressiveness, the terrain of the battle, and many other factors, so in the treatment of heart disease we must consider the character of the disease, its severity, its activity, the complications and the individual who has the affection.

What are the indications for digitalis and how shall we use it? While we are indebted to William Withering who published his treatise in 1785 for the introduction of digitalis to physicians, we have added greatly to our knowledge of its use in recent years.

There are two chief indications for the exhibition of digitalis: (1) decompensation and (2) auricular fibrillation. Perhaps it will be well to amplify that statement. By decompensation we mean the presence or development of symptoms or signs of congestive heart failure from the earliest stage of increasing dyspnea, cough, basal râles, etc., through the extreme state of orthopnea, general anasarca and the like. As already stated digitalis is not indicated because of the presence of cardiac pathological anatomy alone, but on the contrary it is indicated with decompensation regardless of the pathology present. Also, with the establishment of permanent auricular fibrillation digitalis is indicated, regardless of the state of compensation, in practically all cases for the purpose of slowing the ventricular rate and making all ventricular contractions effective; furthermore, digitalis must be continued in appropriate dosage as long as such fibrillation lasts, that is throughout the patient's life unless the fibrillation spontaneously or by the action of such drugs as quinidine changes to normal mechanism. The exceptional case of the naturally slow ventricular rate in untreated auricular fibrillation, probably due

to inherent conduction defects, not needing digitalis merely proves the rule.

The more we know of the action of digitalis, pharmacologic, physiologic and toxic, the better will we be able to use it. Withering working with the crude unstandardized drug clearly understood many of its actions and enunciated a century and a half ago the principles which we still use today. "Let the medicine be continued until it acts either on the stomach, the kidneys, the pulse, or the bowels; let it be stopped upon the first indication of any of these effects." He thus recognized the toxic nausea, the beneficial diuresis and slowing of the pulse in auricular fibrillation, not then recognized as such, the production of extrasystoles and heart block as toxic manifestations together with the occasional diarrhea.

In recent years we have been fortunate in having many well standardized and relatively stable digitalis products and in learning through careful study the average tolerance of an individual. Eggleston in 1915 showed that it required 15 cc. of an average high-grade standard tincture of digitalis (1.5 Gm. of the dried leaf) per 100 pounds of body weight to completely digitalize an individual. While we must not use this figure as an absolute and unchangeable dosage, it does serve as a guide and much of our modern use of digitalis dates from that work.

For several years we have heard much about the standardization of digitalis by cat units and the United States Pharmacopeia has designated that 1 cat unit is equivalent to 0.1 Gm. of standardized powdered digitalis leaf (1 cc. of the tincture), the cat unit being the weight of the dried drug in milligram necessary to kill 1 Kg. of cat in one and one-half hours. While we need not concern ourselves with cat units, we must, however, be sure we are using a standardized and potent preparation.

Whether we quickly or slowly digitalize a patient will depend upon the exigencies of the occasion, both methods having value. Rapid digitalization is indicated when the patient is in severe decompensation and the time element plays an im-

portant part either because of the severity of the symptoms or the danger to life, though many believe that quick digitalization is desirable in all stages of decompensation. However, it must not be inferred from this statement that digitalis is an emergency drug, for this is but rarely the case though it often has urgent indications. With rapid digitalization we must be certain that none of the drugs of the digitalis series have been used in the preceding three weeks, or if used we must take the amount into consideration in estimating the dosage. For a previously undigitalized individual of 160 pounds, whose estimated requirement would be 2.4 Gm. of the powdered leaf (24 cc. of the tincture) the following schedule would provide relatively rapid and yet safe digitalization:

1st Dose,  $\frac{1}{4}$  calculated dose, 0.8 Gm. (powdered leaf) (8 cc. tinc.)  
 2nd Dose, 6 hours later,  $\frac{1}{8}$  calculated dose, 0.4 Gm. (4 cc. tinc.)  
 3rd Dose, 6 hours later,  $\frac{1}{12}$  calculated dose, 0.2 Gm. (2 cc. tinc.)  
 4th Dose, 6 hours later,  $\frac{1}{24}$  calculated dose, 0.1 Gm. (1 cc. tinc.)  
 5th Dose, 6 hours later,  $\frac{1}{24}$  calculated dose, 0.1 Gm. (1 cc. tinc.)  
 Total— $\frac{2}{3}$  calculated dose, 1.6 Gm. (16 cc. tincture) in 24 hours.

The dose of 0.1 Gm. (1 cc. tincture) may be repeated every six hours thereafter until full digitalization has been obtained. For maintenance of full digitalis effect we use approximately 0.15 Gm. of the powdered leaf (1.5 cc. tincture) daily, many using 0.1 Gm. (1 cc. tincture) or 1 cat unit as the daily maintenance dose though this figure is subject to wide variation. The recent trend has been toward the use of the powdered leaf in tablet, pill or capsule form, and in our work in the clinic and hospital as well as in private practice, we have practically discarded the use of the tincture, though it too is very satisfactory if we are sure of its potency and if we always keep in mind the fact that a drop is not a minim of tincture digitalis, there being in fact an average of  $2\frac{1}{2}$  to 3 drops to the minim.

Because most of the pharmaceutical preparations are now prepared in 0.1 Gm. (1 cat unit) size, though some are scored for easy division, we have found it convenient when prescribing a maintenance dose of digitalis of 0.15 Gm. daily to

have the patient take a tablet of 0.1 Gm. one day and 2 tablets the next day, alternately, instead of  $1\frac{1}{2}$  tablets daily, using an ever handy calendar as the guide, taking 1 tablet on the odd days of the month and 2 on the even days.

When rapid digitalization is not indicated, there will naturally be a wide variation in the method of dosage, depending upon individual factors such as degree of decompensation, ventricular rate in fibrillation, frequency of visits of the ambulatory patient, etc., but a satisfactory method for this small divided dose régime is 0.1 to 0.2 Gm. (1 to 2 cc. tincture) two or three times daily, until digitalis effect or toxic effect is observed, then reducing the daily dose to the maintenance level, 0.15 Gm. (1.5 cc. tincture) daily. Again, I must emphasize the fact that a drop is not a minim. A clear understanding of our aims in digitalizing and of the toxic effects of digitalis is necessary for best results.

Aside from the rare use of strophanthin in doses of 0.5 mg. (not over 1 mg. daily) intravenously in emergency cases, a use not wholly unattended by danger, we need consider but one other member of the digitalis series.

Recently an active cardiac glucoside with digitalis-like action has been isolated from the bestill nut and given the name, thevetin. This active principle has been tested and its potency and toxicity have been shown to be one seventh that of ouabain. It too is standardized in cat units and is obtainable in 2-cc. ampules containing in solution 0.00275 Gm. ( $\frac{1}{4}$  grain) of the active drug, equivalent to 3 cat units. We are at present maintaining adequate "digitalization" by giving one such ampule (3 cat units) intravenously every other day. This drug at present can only be given intravenously and whether or not it will maintain a place in our armamentarium remains to be seen.

Ranking with digitalis and equally necessary in the treatment of the cardiac patient is rest, varying all the way from simple limitation of activity to absolute bed rest, the latter so valuable in the severely decompensated case. Care in securing and assuring this rest is very important, and attention

to detail is well rewarded. It is the very exceptional, in fact one might say almost unique, patient who cannot remain in bed, though many attempt to convince the physician that they must sit up in a chair; and herein lies the value of adjunct treatment with sedatives, hypnotics, and opiates. A good rule is to begin the bed treatment (either at home or in the hospital) of the severely decompensated cardiac with a hypodermic injection of morphine (10 to 15 mg.,  $\frac{1}{8}$  to  $\frac{1}{4}$  grain) for the first two or three nights and then substitute a non-narcotic hypnotic. At certain stages in treatment the anxiety state of the patient plays as important a rôle as the myocardial insufficiency and proper sedation is extremely valuable.

While digitalis and rest will usually produce an adequate diuresis, there are some patients whose edema persists despite these measures. For such patients we have a group of diuretic drugs which are very helpful in the continuation treatment of myocardial insufficiency. Usually we do not prescribe these diuretics until the patient has become fully digitalized but occasionally when the edema is of marked degree we may use the diuretics at the outset along with digitalis and rest. There are a large number of diuretics on the market but our experience has led us to rely upon but few of them in producing adequate diuresis. Despite the frequent mention and use of theobromine-sodio-salicylate (diuretin) or theobromine-calcium-salicylate (theocalcin) we have not obtained (except in very rare instances) an effective diuresis with the usually recommended doses 0.5 to 1 Gm. ( $7\frac{1}{2}$  to 15 grains) three or four times a day or even with much larger doses of 6 to 8 Gm. (90 to 120 grains) daily.

On the other hand we have often produced a beautiful diuresis with theophyllin (theocin) given in doses of 0.3 Gm. (5 grains) three times a day for two days, omitting two days and repeating. Unfortunately this effective dose usually produces undesirable side actions, nausea, vomiting, headache and increased irritability, so that experience has taught us to prescribe it in smaller dosage 0.2 Gm. (3 grains) in the manner above described. While the diuresis with this dose is usually



not as great, it is still effective in many cases. Even with this dose increased irritability and headache may occur, especially on the second day of administration and we have attempted to overcome this undesirable effect by combining it with a small dose of a sedative, as for instance, phenobarbital 0.015 to 0.03 Gm. ( $\frac{1}{4}$  to  $\frac{1}{2}$  grain), or amytal 0.03 to 0.045 Gm. ( $\frac{1}{2}$  to  $\frac{3}{4}$  grain) with each dose. Such combination usually is effective in preventing these side actions.

As effective as has been the diuresis from theophyllin, in just opposite measure has been our experience with its double salt, theophyllin-ethylene-diamine (aminophyllin, metaphyllin, euphyllin) which in doses of 0.09 Gm. ( $1\frac{1}{2}$  grains) three times a day, or double this dose has only rarely given us effective diuresis. I do not refer here to the use of this drug as a coronary dilator, but merely as a diuretic.

Lately some claim has been made that aminophyllin properly administered will relieve Cheyne-Stokes respiration in myocardial insufficiency, a claim that if proved will be of great value in our treatment as Cheyne-Stokes breathing is often one of the most distressing of symptoms in cardiac decompensation.

Since the introduction of the mercurial diuretics, we have come to look upon them as the most dependable. The original one, novasurol, has been replaced entirely (because of greater effectiveness and less toxicity) by salyrgan and mercupurin, the latter of more recent introduction, being a mercurial and theophyllin in chemical and free combination. Both of these diuretics are very effective often giving a diuresis of 3000 to 8000 cc. in twenty-four hours, the complete diuresis usually being only of this duration. These diuretics must be given intravenously (preferably) or intramuscularly, never subcutaneously and are given in doses of 1 to 2 cc. at intervals of a few days or longer as needed. An original dose of  $\frac{1}{2}$  cc. is usually given to test the patient's susceptibility.

The effectiveness of salyrgan and mercupurin is usually enhanced by the previous ingestion of ammonium chloride (or nitrate) in doses of 4 to 8 Gm. (60 to 120 grains) (enteric-

coated tablets) daily for three to four days before the mercurial injection.

In the hands of some, urea in large doses (15 to 60 Gm. daily) over a long period has been effective as a diuretic but we have found much objection to the taste and have not found it as effective as theocin, salyrgan, and mercupurin. The latter in most cases of myocardial insufficiency has been the most effective diuretic, especially when given after ammonium chloride.

Occasionally a hypertonic glucose solution (50 to 100 cc. of a 50 per cent solution) is effective as a diuretic, especially when there has been a temporary suppression of urine as in the circulatory shock and failure following coronary occlusion, but glucose has not come up to expectation in general experience. Perhaps it has its greatest usefulness in the cardiac failure of diphtheria. When such a hypertonic solution of glucose is given intravenously, great care must be taken to have the solution at body temperature and to inject it very slowly to prevent venous thrombosis.

Speaking of glucose brings up the subject of diet in the treatment of myocardial insufficiency. The high carbohydrate Smith cardiac diet usually has to be modified as most patients will not take the full diet without complaining of its sweetness. Recently emphasis has been placed on a low caloric diet (following the now current vogue of keeping metabolism at a low ebb) in myocardial insufficiency but we have not yet been convinced of its value, except perhaps in the early stage of treatment (not for a prolonged period) and in the obese. The old Karell diet still has its place in the severely decompensated patient with marked edema but this diet must not be continued for more than a few days.

Generally speaking, a diet adapted to the bedridden patient—whose appetite is usually poor—and which is correctly balanced is the proper diet. This means adequate protein for nitrogen balance—50 to 60 Gm. on the average—and ample carbohydrates with attention in the long drawn-out cases to the necessary vitamin, caloric and mineral (iron especially)

content. The food should be easily digestible, and in the case of very sick patients, should not require much chewing. Limitation of fluids to 1200 to 1500 cc. in twenty-four hours is usually desirable when edema is present, but due consideration must be given to the patient's comfort, especially in very warm weather or if there is excessive sweating. Limitation of salt intake is helpful when edema persists and the substitution of potassium salts may have some value.

If hydrothorax or ascites persists and is of considerable degree paracentesis will be found useful and may be repeated as often as necessary. Since the advent, however, of the stronger diuretics, tapping does not have to be resorted to as frequently as formerly. While Southey tubes to drain subcutaneous edema were described in 1877 and are always mentioned in articles on treatment of heart failure, they are but rarely needed, in fact I personally have never used them.

When dyspnea is marked, particularly if accompanied by marked cyanosis, inhalations of oxygen from a tent or by nasal catheter will usually lessen the cyanosis and often decrease the dyspnea.

Venesection (400–600 cc.) will sometimes be of value in relieving the dyspnea of myocardial insufficiency, but should be used only in the plethoric individual who shows venous and hepatic engorgement and in the case of acute pulmonary edema, characterized by urgent dyspnea, hacking irrepressible cough, frothy blood-tinged sputum, cyanosis, clammy skin, etc., which has not been relieved by immediate injection of morphine  $\frac{1}{4}$  grain and atropine  $\frac{1}{100}$  grain, repeated in twenty to thirty minutes.

The use of caffeine sodiobenzoate (1 ampule, 0.5 Gm. [ $7\frac{1}{2}$  grains]) intravenously whenever there is evidence of a failing pulse, weak, rapid, thready, seems to be of value and may be frequently repeated to tide over a crisis. Similarly adrenalin injections—5 to 10 minims of 1:1000 solution intramuscularly—occasionally intravenously slowly as with 500 to 1000 cc. of 10 per cent glucose, and more rarely directly

into the heart after cardiac standstill, may act as a powerful stimulant in an emergency.

Quinidine must be mentioned in a review of the treatment of myocardial insufficiency though it will have but a small place therein. In the rare case when the heart rate in auricular fibrillation associated with cardiac decompensation cannot be properly slowed by digitalis, rest, etc., quinidine may be of some value though too much should not be expected in such a case. Likewise when heart failure supervenes on an attack of paroxysmal tachycardia, the use of quinidine to stop the attack and lessen the cardiac burden is definitely indicated. Quinidine, which is used as the salt, quinidine sulphate, causes toxic effects in some people even with small doses; therefore the patient should always be tested for idiosyncrasy by a small initial dose of 0.2 Gm. (3 grains). After that it may be given (usually in capsules) in a dose of 0.3 Gm. (5 grains) and thereafter 0.6 Gm. (10 grains) three times a day, if the toxic symptoms of diarrhea, nausea, vomiting, tinnitus, vertigo, headache, weakness, or fainting do not occur. In an emergency even larger doses may be used.

Today no discussion of the treatment of heart disease is complete without mention of total ablation of the thyroid as described by Blumgart and Levine and their coworkers. While the reported results have given rise to some promise and while the results we have had here in St. Louis have been a mixture of good and bad, we must still keep this procedure sub judice. My own feeling at present is that time will probably prove total thyroidectomy too radical and too uncertain a method to have much of a place in the treatment of myocardial insufficiency.

One phase of the treatment of myocardial insufficiency that is frequently completely overlooked and often given too little attention is the use of occupational therapy. The patient with heart disease is apt to be moody and introspective and needs an interest and outlet such as may be provided by occupational therapy. Reading was formerly the chief reliant of the cardiac patient but with the advent of radio broad-

casting a new large field for diversion was opened to the partially incapacitated person. But in addition to these measures, rightly included in occupational therapy, we have the stimulating handicrafts which widen the outlook and interest of the handicapped individual. Occupational therapy does more, however, by providing means for testing and training the patient with heart disease so that he may serve to his full capacity and not be handicapped by fears and prohibitions. Even in Class III patients, except in the very acute stages or in the terminal stage of heart disease, absolute rest is rarely required or desirable. In fact absolute physical rest with mental perturbation may and usually does result in greater strain on the circulation than mild physical activity and peace of mind so even in this group occupational therapy may be of great help.

Finally, a careful consideration of the entire social-economic status of the patient with heart disease must form a part of the scheme of treatment, for the difference between complete success and partial failure may depend upon a proper adjustment of these factors after the measures previously discussed have been provided.

## CLINIC OF DR. SIDNEY I. SCHWAB

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### NEUROSES AND PSYCHOSES AS THE GENERAL PRACTITIONER SEES THEM

THIS clinic attempts to do three things: first, to point out the present conception of the clinical types included under the terms neurosis and psychosis. Second, to suggest that the general practitioner or internist can recognize these diseases in their early and initial form. Third, to give brief clinical descriptions of cases which eventually tend to develop into one or another of the various types to which this classification applies.

The importance of attempting to describe these things from the standpoint of the general practitioner is obvious when the position which he occupies in relation to the general spread of illness is considered. The great percentage of all practitioners of medicine belong to the general practitioner class. From 60 to 70 per cent of all sick people can be roughly grouped as having a neurosis or psychosis either as a primary or secondary condition. That is to say in the great majority of sick people the preponderant clinical expressions and symptoms are due to the effect of disturbances, whatever their cause may be, on the functional integrity of the organism. In a very large proportion of all illness the effect of the illness is less to be noted in the organs and systems of the body than it is upon the individual as a whole. Illness of whatever nature shows its effect chiefly in disturbance of conduct, disturbance of feeling, disturbance in the capacity to

maintain a proper adjustment to the environment. From the standpoint of the patient whatever his description of his illness may be its effect upon him lies largely in a sense of incapacity or the demonstrable defect in his ability to work, in his inability to live up to the level of his social and economic necessities. For the patient this is the principal evidence of illness. The practitioner of medicine in this sense sees such instances of illness as a primary contact. Inasmuch as he represents by far the great majority of physicians he must necessarily see a great majority of such patients. These patients therefore represent by far the most important material for the incipency of the neurosis and psychosis.

The specialist in neuropsychiatry sees such cases, as a rule, as they filter through the preliminary stages of this and that specialist and finally as a sort of last resort are received into the small group of cases which can be taken care of by a comparatively small number of men, and can only be intelligently treated in comparatively small numbers. By that time in most instances the neurosis or psychosis is well fixed and crystallized and the therapeutic problem is one of prolonged and tedious treatment. It is important to get an understanding of these conditions as developed in the more specialistic levels into the levels represented by those physicians who in the nature of their work see such cases earlier and form frequently the first contacts with them. It is far more important, from the general welfare of the public and from the point of view of communal health, that the practitioner should grasp and understand the vital concept of the neurosis and psychosis than it is to develop a highly trained group of specialists who have neither the time nor the opportunity to take care of the great mass of people who are permanently or temporarily handicapped by these conditions. This is not to say that there should be any artificial limits in the number of neuropsychiatrists that are needed in any one community or that there should be any backward step in the primarily cultural, medical and postgraduate training of such a group. The point is made here, however, that until the non-

specialist group become infiltrated with the necessary and primary knowledge of these conditions the existence of a group of specialists will not begin to solve the neuropsychiatric problems in any community.

What medical training and education should seek is to provide for each student graduating from the medical school a grasp and insight into the mechanism of the neuroses and psychoses so that he will be able to see them as they first show themselves, to recognize them as clinical entities, and to treat them as such. The cases that do not respond to such treatment or those which represent the more complex situations will naturally drift after a while to the specialist, always marked, however, with the evidence and traces of an intelligent, well-informed and sympathetic contact of first instance. That is to say such would be the expected result if the simple and elementary principles underlying the origins and development of the neuroses and psychoses were understood and if the general practitioner as a part of his interest and activity could be persuaded to become as much interested in instances of these diseases as he is in the more common so-called "organical" conditions.

The training of the specialist is provided for sufficiently in our best medical schools or is in the course of being so provided. The training of the average medical man who is to become a general practitioner and internist is at present woefully deficient in this respect. This deficiency does not appear to be due to any lack of understanding of the importance of these conditions, but rather to a shifting emphasis from the more common states of illness to those of a rarer and specifically more interesting sort.

It is curious that the most common condition affecting mankind, that is, the defective working of his complete organism in terms of personal and environmental adjustment or in such distortions of his personality leading to the same result should be so completely ignored in the usual training of a medical student and should be so completely wanting at least in the sphere of interest in the average practitioner of medic-



ine. This criticism is not directed to the training in neurology and psychiatry in our best medical schools, which on the whole is ample enough, but to the fact that the knowledge gained there of these conditions is not carried through and out into the actual life and experience of the physician in general practice. There are many efforts to correct this seeming paradox by the organization of lectures, talks and postgraduate courses, by various societies and movements, mental hygiene, etc., but primarily the nucleus of the effort must be found in the early instruction of the medical student and by a resourceful and continuous effort to make of these conditions something as tangible, important and practicable as are the other branches of medicine.

There are several things that naturally spring out of this conception of the important rôle played by the neuroses and psychoses—one is that they are clinical entities—not perhaps as rigidly outlined as some other entities. The other is that they can be recognized in their incipency as the beginnings of other diseases can and that they form an important part of almost any kind of illness no matter what the nature of that illness may be. There is a psychiatric or neurotic background or even an extension of their mechanism expressed in symptoms in almost any one who is the victim of an organic change in his body as a whole. These neuroses or psychoses reactions or background may be expressed either as a local or as a general manifestation. Such manifestations may well be included in the classification of neuroses or psychoses as early or initial symptoms of these conditions. At times these are symptom reactions which are temporary and of an episode character and they disappear then as the general internal disease disappears or is cured. In other instances, however, they represent the very early beginnings of a later developed much more profoundly built up neurosis or psychosis.

How is it to be known that an individual who presents himself with complaints or symptoms usually described as localized in systems of his body is suffering from an early neurosis or incipient psychosis in spite of his obvious com-

plaints, as for example, headache, insomnia, indigestion, pain, muscular disability, etc.? It is necessary to know what these things are. Is it possible to reduce them to a more or less simple formula? The masking symptoms or complaints obliterate the underlying psychotic or neurotic manifestations. It is obvious that here the general practitioner could be most useful in finding out much more about the individual by seeking to extend his scrutiny beneath the description of the patient's own complaints.

The first thing is to get some notion of what psychoses and neuroses are. Is it possible to reduce them to a more or less simple formula containing insight into the mechanism, causes and developments?

A neurosis is in the first place a clinical syndrome, a built-up series of unusual and abnormal reactions. The patient is aware of this and he can describe his abnormal sensations, feelings, and can attach them to organs, functions and systems of his body. To the outsider, to his physician he may not present the appearance of a sick person, but to himself, which after all is the focal point of interest, he thinks, believes and is convinced that he is sick. On physical and laboratory examination there may be few or no data of an unusual or abnormal kind, certainly not those commonly associated with severe illness and as a rule the amount of disability which the patient is aware of is out of proportion entirely to the meager if any positive findings on examination. It is often this discrepancy which strikes the examiner as the most outstanding result of the examination. It is again this discrepancy which should suggest the existence of an illness not ordinarily defined in terms of objective changes. This discrepancy means in many instances the possibility of a neurosis. On the other hand no neurosis of any consequence escapes objective demonstrable clinical expressions of illness. The findings which can be determined by the ordinary physical, neurological or psychological studies are such as can be described and objectively determined. They consist of a group of symptoms that point to something that is called, and has been for a long time—

functional. A better term would be unphysiological. The paradox of a normal heart, for example, with tachycardia, a normal cardiographic pattern with dyspnea, pain, constriction about the chest and other indications of a defective heart mechanism. Fatigue in the presence of good muscular power. Visual deficiency in the face of normal retinal acuity and muscle findings. Headache and the accompanying invalidism with normal x-ray sinus examination. This discrepancy between findings and the burden of symptoms is generally striking and imposing. So much so that to the average physician the whole thing seems unreal. Here is a patient sick, incapacitated and handicapped and obviously in distress. What then is the chief mechanism which is capable of producing such a widespread disturbance in the functions, activities and in the physiological and chemicophysical organs, systems and organizations of the body? It must lie in the controlling and integrating mechanism of the body rather than in the structures themselves. It must be associated with causes which act particularly upon this mechanism and to which this mechanism is sensitive and for which such a system is automatically and physiologically planned or developed to respond. The nervous system and particularly its vegetative component represents in its distribution, control, widespread universal participation in all parts of the body an ideal mechanism to respond to what may be called emotional or feeling components. Perhaps the whole of this may be better understood if the term sensation is meant to be all-inclusive.

Emotion is the primary mechanism which actuates the total instinctive self-preservative functions of the body to act in forms of conduct which protect, safeguard, adjust, compromise and guard the personality against the whole of the environmental incidents, concurrences, happenings. When the resulting conduct is achieved then the emotion has fulfilled its function and the individual has transferred his emotion successfully in terms of conduct which has solved more or less completely and more or less successfully a particular situation. Such things are not neuroses situations. When

the conduct performs nothing tangible in terms of solution but results in nothing more than the production of what are called symptoms, then the situation is not in terms of an adjustable piece of conduct or performance, but the safeguarding lies in the organization of an illness under whose protection the patient is safe or guarded. He is so because he is sick and the inner conviction of illness defends him against a further difficulty in environment which in the first instance disturbed him. Fears, anxieties, apprehensions, states of panic are all noted as the precipitating agents of this disturbance of the individual's life. The organism spills out through the vascular system, glandular secretory system, energies which fail to produce adjustable conduct, but do produce disturbances in control and functional integration. Therefore the patient shows symptoms and findings demonstrable by the ordinary physical examination and in addition that inner state of tension resulting from emotional stimulation which has no avenue of external expression in terms of conduct. The sources of this distortion lie in conflicts, many of them unknown to the patient, many of them unconscious. Such conflicts have to do with the social, economic, erotic and personal life of the individual neurosis victim. This conception may be summarized in this way. The neuroses are clinical pictures, symptomatically organized, producing objectively recognizable physical abnormalities caused generally by disturbances in the function of an organ or system independent of gross anatomical structure changes. They arise from personal conflicts. They defend and protect the individual from the consequences of personal situations that he cannot solve other than through an illness. Most of these mechanisms are unconscious, though it is frequently impossible to draw a line between the two levels—the conscious and the unconscious.

This conception of the neuroses, which has been the outgrowth and development of many schools of thought and may be approached from many diversified types of etiology and mechanism, stands out as showing two things. First of all the reality of the neurosis and secondly the individuality of a

neurosis, that is to say, that each individual with a neurosis is an expression of that individual and no other, and consequently the study of a neurosis means primarily the study of the individual as a separate and distinct personality. This conception also provides for the general practitioner and internist a conception of the neuroses that is tangible and has its clinical expression that can be studied in the same way that any other disease can be. The symptoms and findings of such conditions can be tabulated and examinations made as part of the ordinary physical examinations, as in all instances of a neurosis is shown some disturbance in the function of the important and primary systems of the body. If no evidence of abnormal functioning is demonstrable then the chances of the patient having a neurosis are extremely small. The fact of the tachycardia, tremor, evidence of metabolic disturbance, and various kinds of pain, muscle disabilities of various sorts in the presence of negative laboratory and physical findings should not be passed by as something of no value, intangible and utterly beyond explanation, but should be understood as intimately as our knowledge provides of the general physical mechanism of the human body. In this sense they are symptoms and out of these symptoms are built clinical entities capable of tabulation and description.

A psychosis is a much more profound disturbance of the whole of a man. It is difficult to see evidence of the self-preservative instinct but rather the reverse is evident.

In the psychosis there is frequently definite organic changes in the structure of the nervous system, in the vascular system and in the neuron system of the brain. These produce alteration of conduct, disintegration and distortion of intellectual and emotional expressions all the way from serious deterioration and almost total intelligence defect to such a disturbance in mental organization that the individual is unable to make use of his knowledge, experience and articulate expression in line with his former intellectual and social level. Such gross disturbances are not difficult to recognize clinically and need not be described here in any detail. The so-called

"functional" psychoses are not removed in point of mechanism from the neuroses other than they involve less adaptation to experiences than a destructive and antagonistic attitude to them. The essential symptomatic expression of the emotionally derived reaction in terms of conduct may be found in both the neuroses and psychoses. The essential difference in a broad clinical aspect is that in a neurosis there is always an element of compromise and personal safeguarding while in the psychosis the examiner feels a sense of the destruction of personal adaptability, of a drive toward an injury to and final death of the personality. The victim of a delusional system is driven to acts or thoughts and plans of acts antagonistic to physiological safeguarding. The organized self-preservative mechanism so painfully built up through evolutionary experiences and reinforced by the individual's education and personal experience seem in many of the psychoses almost nonexistent and generally noneffective. For example, the obvious defective conditions of the functions of the body as a whole seen in depressive states producing nutritional defects of a serious nature cannot be viewed as in any way a safeguarding mechanism of the personality. The sense of unreality, so common in the symptomatology of an early psychosis, may be thought of as a sort of primary concept into the understanding of many a psychosis.

Aside from the study of content of consciousness, ideas, theories, concepts, etc., the victim of a psychosis presents many physical and symptomatic expressions of distorted physiological function; respiration, shallow, slow; nutritional defect; disturbance in the gastro-intestinal system, cardiac, vasomotor and excretory systems, etc. Metabolism is often disturbed and the psychotic as well as the neurosis patients are in the last analysis material for internal medical scrutiny as certainly the preliminary step toward understanding or anticipating the final psychotic crystallization into the chronic and inevitable hopeless state of the final stage of mental disease.

The psychoses in many ways show as initial symptoms

primitive and infantile types of conduct, reversion to primitive forms of escape, lethargy, stupor and sleep states, a feigning of death seen in animal-like stupors, a kind of situation hibernation. These early evidences of psychosis seen in the beginning of schizophrenia, for example, suggest that the sub-cortical mechanisms at the infantile level are working at the expense of the more cortical, more adult levels. The forgotten, submerged, primitive kinds of conduct cover the adult, more mature reactions, leading to nonorganized, unrelated infantile responses. The adult formulae are temporarily out. Among other things that can be noted, recorded and observed are frustration, the tendency to exist in the atmosphere and security of early experiences at the infant or child level, the building up of a conviction of hopelessness as far as the biological struggle to equalize the conflicts of a social, personal, economic, sexual kind. The outside world, the world of reality, becomes a distorted unreal world. Unreality becomes the characteristic of the world outside and reality of the world inside. There are the perverted sensory responses, hallucination, delusioned structures weighted with the tangibility and the realistic features of awareness. Infantile, childish material, the repressed experiences of that period are relived until they become the stuff of the activities of consciousness. Wishes, desires and day-dreaming phantasies become distorted into facts, the material of actual experience.

The psychosis and neurosis are characteristic clinical responses to difficult situations in the life of many individuals. The neuroses tend to tide them over under the protection of illness clinically recognizable and clinically demonstrable. The psychoses are likewise clinical responses of perhaps antagonistic types as far as the life situation as a whole is concerned. The psychoses are more profound personality disturbances and the mechanism of protection is less clear and has destruction rather than safeguarding as its characteristic.

It is also clear that in either group or in a combination of the two in one individual the conditions as such should not and cannot be divorced from the general aspect of internal

medicine. In any case of neurosis or psychosis the presence of actual disturbance in the functions and systems of the body should be inferred rather than ignored. The mind and the body are to be thought of as one and there is no disturbance of either that can leave the body as a whole unaffected. In other words the neurosis or psychosis or any combination of the two are primarily problems for the doctor interested in treating sick people and those whose function it is to take care of unselected groups of the sick in whatever social levels their activities are directed are the ones who see these cases in the earliest stages when understanding, guidance, explanation and simple medical planning may be effective in the prevention of the final crystallization of these states into chronic fixed and inelastic diseases of the personality.

Personality is defined here as simply the man in action—man living as a social being in a complicated difficult social structure. Sickness is one of the experiences that make him less fit to live in this respect and in particular illness of his nervous system producing primarily a less efficient integration as shown principally in less efficient conduct which is called the neurosis or psychosis. The general practitioner is logically the one who seems these things first, sees more of them, and sees them in the beginning, sees the early fragmentation of personality and should therefore be the one especially sensitive in a clinical receptive sense to the existence of these symptoms in his patients.

The last part of this will be devoted to a brief history of cases in which the essential neuroses or psychoses as clinical pictures are masked under the appearance of disease as evidenced by the presenting symptoms and complaints of the patient. These are the difficult problems which the practitioner has to face, namely, to see the early evidence of a neurosis or psychosis beneath the mask or screen of what at first appears to be gastro-intestinal, cardiac, respiratory or any other kind of illness.



## CLINICAL EXAMPLES

Examples to illustrate the ideas of the neuroses and psychoses are not given as complete clinical reports but rather as sketches which attempt to reflect the clinical pictures as they might or have been presented to the internist or general practitioner as first instances, and as a contrast to the clinical pictures which they presented to the psychiatrist in a more completely developed type of disease.

**Case I.**—This is a married woman, thirty-four years of age. The marriage has been childless. The cause of the sterility is said to have been a congenitally small and pathological narrow vaginal outlet. As seen by the psychiatrist she presents the picture of a profound emotional disturbance with fears, apprehensions, anxieties and frequently occurring states of panic in which she is unable to carry out any practicable type of conduct in line with a situation necessitating some sort of action, that is, getting on a train, going to visit some one, meeting an appointment, etc. However she is always able to see a doctor and keep her appointment promptly. She has developed a feeling of security in the presence of a physician, whether her own or a stranger. It is noted that this patient is alert, intelligent, well-educated and responsive. She comes from people with fine cultural background and fine personal traditions. She married a man who is a chronic alcoholic.

Her past life has been filled with difficult situations—personal, family, domestic and economic. One brother is a manic-depressive. He lives with her in a distant city during his less excitable periods. Several members of her family have shown psychotic episodes, her father had several depressed episodes in one of which the writer was his physician.

Her chief complaints of a physical sort are tachycardia, loss of weight, and a history of numerous gastro-intestinal symptoms suggesting appendicitis, acute food poisoning, etc.

This sketches the situation as it now is—an individual

whose reactions are patterned and whose personality distortion reflects an emotional framework chiefly of the depressive type. Her total reaction has become so stereotyped that although she faces many different situations her response to them is generally psychotic. These responses are generally in the framework of a psychosis with definitely outlined clinical features resembling the depressed phase of a manic-depressive psychosis. The beginnings of the present situation were present when she was first seen by the family doctor at an early age. At that time she was an erratic, very intelligent child, given to emotional excessive reactions under very minimal stimuli. At an early age she was aware of the domestic conflicts between her parents. She was torn between her admiration for her father and her love for her very beautiful mother. At about the age of twelve her mother was divorced and she and her brother were in the custody of the mother.

The first of the acute gastro-intestinal attacks took place about this time and in each and all of these, extending through a period of many years, the diagnostic efforts were exclusively directed toward the gastric symptoms which tended to cover the underlying psychiatric situation almost completely. It was early noted by those about her that the most unusual features of these attacks were that the vomiting and diarrhea as well as the tachycardia and weakness appeared to subside with great promptness whenever a physician was present or upon her entrance to a hospital. She was many times taken to the hospital as an acute abdominal emergency. Several times she had been prepared for abdominal exploration and on each occasion just before the operation or upon her entrance to the hospital the acute gastro-intestinal symptoms stopped suddenly and the patient felt quite well. When she was twenty she had her first serious psychosis and was confined in a psychiatric institution for six months. This and a recent institutional experience of two months are the only sanatoria admissions.

Physical and neurological examination made of this patient just about two or three hours after the symptoms of her

latest gastro-intestinal attack ceased showed no significant findings. Outside of the slight loss of weight in the last two months she seemed physically well.

The point of this sketch lies chiefly in the first contact period with the general practitioner. It illustrates the vital importance of this early contact, presenting at least at that time an opportunity for an intensive study of this individual outside and apart from the acute abdominal symptoms for which in many instances the family physician had been called. It might have been obvious, though this is said with no degree of certainty, that the gastro-intestinal symptoms might have been recognized as purely functional or an emotional escape through which the pent up feelings gained in this way some sort of physical expression. Perhaps in this as in other cases this was understood by the physicians who saw her in her early years, but the fact remains, however, that whether recognized or not nothing was done in the way of explanation, guidance or change in the environmental relation of this patient to alter in any way the conditions which produced not merely the gastro-intestinal symptoms but laid the foundation for the future development of a psychosis. This patient has been examined at least fifteen times in various hospitals and clinics throughout the country for evidence of gastro-intestinal disease. She has been x-rayed many times. Nothing ever was found to account for the gastric symptoms. All other examinations have been equally without findings.

It is evident in this short account that the period of greatest therapeutic possibility was during the years of early medical contacts. These contacts naturally with physicians who had no particular specialistic knowledge of psychiatry or neurology. Yet there is the possibility that if the importance of understanding something about the personality of the individual who was sick had permeated down through the levels of sickness caused by so-called "organic" causes this individual might have been seen, dimly outlined it is true, as the psychiatric figure which she developed into at the age of twenty with a psychosis which at that time was manifesting itself and

crystallizing into the clinically patterned form which she shows at the present time.

**Case II.**—This is a man forty-five years old, who came into the Barnes Hospital after a preliminary office visit with a chief complaint of shaking of the right hand. This goes back some ten or twelve years. It had been diagnosed as paralysis agitans by a number of doctors. The patient is an intelligent well-trained minister who has obtained a Ph.D. in English at a western university. The physical examinations at Barnes are essentially negative. In addition to the tremor of the hand a definite hemihypesthesia with sharp midline distribution from the top of the head, bisecting with accuracy the body half is found. A history of an automobile accident and compensation involvement is obtained. It is noted that the tremor in the hand becomes much more marked when the compensation question is gone into and when the details of the litigation are mentioned. The tremor was not thought to be of the parkinsonian type and the diagnosis of a neurosis with hysterical features was made. In the short time the patient was at the hospital many instances of conflict, personal disappointments and other difficulties going back to his early college years, his early adolescent and preadolescent years were obtained. There was also the question of honesty in handling funds which were entrusted to him in one of his college positions. The most outstanding of the adult characteristics as shown in the development of symptoms were the accumulation of conflicts, the difficulty in personal adjustment, the frustration of his aims and objectives and resulting dissatisfactions. Patient feels deeply that he was trained and prepared for important teaching positions, as an academic figure and as a religious leader. For each and all of these things his record was always a failure. Behind all of this was his domestic conflict and the necessity he feels of being at home as little as possible. The precipitating factor in his present neurosis was the slight trauma sustained in the automobile accident. Tremor, muscular and vocal fatigue with the hemiplegia are

the objective indications of his neurosis. Here then is a well-developed picture of a neurosis developing in late adult life precipitated by a trauma with litigation features.

Obviously this clinical reaction has its origin, possibilities and roots in early childhood and adolescence. There is only vague information of his early illnesses and only the faintest hints at early medical contacts. There were the usual childhood diseases with symptoms evidently always exaggerated. The environmental influences in which this boy grew up, the conflicts between his own parents, the desire to escape their fate and their low social and economic attainments through education and training could no doubt have been ascertained if such things could be associated with or weighed by medical importance. There must have been many opportunities in the early medical contacts where identification of personal characteristics as favoring the development of a future neurosis could have been made. Even so brief a study of his childhood and adolescent life as could be made in the hospital showed that in almost every difficult situation in life, in almost any situation of a conflict nature, the patient was unable to realistically face them and even in his early childhood had taken refuge in symptoms as a conscious effort to escape responsibility, to escape effort and eventually to escape criticism. These early patterned activities are the stuff out of which the neurosis of an adult type was fashioned. The point is stressed that the possible recognition of these things might have been of value in directing this patient's training and early career in school and college. It is admitted that many of these things were not capable of being corrected, but it is also possible that if this patient had in his early years been able to see himself as he really was and if the patterns of action were noted by his physician as a part of the personal study of this individual then at least this individual might have had an understanding by which he could have modified his actions on a more adjustable level.

**Case III.**—A childless woman, forty-one years of age, married thirteen years. Her husband is a successful business

man and while he has had to work hard there has been little economic stress in the lives of these two people, and certainly none in the last few years.

When first seen she was obviously depressed, inarticulate, introverted, anxious and not a little suspicious. She did not want to see me or any other physician, saying with a good deal of conviction that her sickness was not such that any doctor could either cure or help. Her chief complaints are rapid beating of the heart with sensations of jerking, fatigue, inability to sleep and a state of utter emotional indifference to her husband, parents, relatives and friends. She believes that she has an incurable disease and that she will soon be dead or spend the rest of her life—which will not be long—away from her husband in some place which she is unwilling or unable to describe. She admits that she always had fears of sickness and fears of doctors with whom she has always associated the dire results of illness which in her case seems to have been centered around the fear of tuberculosis.

She was persuaded to enter the Barnes Hospital which she reluctantly did, saying she did so only because her husband insisted. The neurological and general physical examinations showed only insignificant findings—slight tachycardia, some loss of weight, great fatigue on slight muscular effort. Cardio-graphic studies, basal metabolism, etc., were normal. She showed no gross intellectual defect, but was emotionally on a low level, showing feeling only when she described her symptoms, chiefly pertaining to her heart and lungs. Then she would become momentarily more alert and animated. It was clear that in the fancied presence of these severe diseases, the solution of her difficulties was to be met. The wish to be dead was to be accomplished through the natural process of a fatal illness and not through suicide. She would conclude almost any conversation with such phrases as, "I have been such a failure in the past that things will never be the same." "I can never be what I should be." "I am indifferent to my husband as I am to others." She lists the diseases she fears most as tuberculosis, heart disease, cancer of the breast, fear

of choking to death. The fear of these diseases and the wish to be dead of them represents one of the many conflicts which distorted the emotional and intellectual life of this patient. It is evident also that the feeling of an almost total inadequacy and incapacity had developed out of the beginnings of this process extending back to the early years of her married life and back of that to her young girlhood and childhood. She described many fears, of high places, of going to pieces, of not accomplishing things, of making up her mind, of arriving at decisions, of meeting strange people, of being hostess at her home to the friends of her husband. He in order to protect her took on himself most of the duties and responsibilities until she became completely dependent upon him—thus increasing her sense of personal futility and emphasizing her sense of personal inferiority (this is only the briefest sketch of the many mechanisms at work in producing a psychosis). Depression, listlessness, emotional indifference, a state of recessiveness, a total loss of interest in the external world, introversion, and a negativistic attitude resulted. A wish to die instead of to live and a constant fear of disease. Back of all the mental and emotional distortions were the constant symptomatic picture of heart, lungs, eyes, gastro-intestinal distress, weakness, loss of weight, etc. These are the common descriptive terms of almost any kind of illness and were the masking of serious personality difficulties by evidence pointing superficially to well-recognized organic disturbances.

The first contacts of this patient with the family physician were in the nature of acute throat conditions. There were many instances of tonsillar infections in which choking sensations were much exaggerated. There were many examinations of her heart and several remembered bits of medical caution about the effect of these infections upon the heart. Tonsillectomy was advised but was never done because of her fear of choking to death. A period of lung symptoms with the phantom of tuberculosis was remembered as a pretty constant experience of her late childhood and adolescence.

She grew up in a very rigid, tight, inelastic atmosphere,

narrowly religious, a household permeated with a sense of obligation and duty, a masterful father and a dominated mother. She had little freedom, only selected playmates, and no social contacts outside a few family associates. No sex instruction and no questions allowed. This with many other questions vital to a growing adolescent girl were taboo. Marriage was to her a prospectively terrible experience, which, as a matter of fact, she postponed several times in states of panic and fear. It is not necessary to more than mention the framework of this patient's early years to suggest that there were the beginnings of the psychosis described in the latest psychiatric contact.

It would seem evident that the opportunity was presented to the general practitioner who first took care of this patient in those earliest years to at least have identified the personality characteristics of this type of child as being the stuff out of which a future neurosis or psychosis might develop. Very likely the physician vaguely did recognize this and felt powerless to do anything about it. Here again the opportunity at least is stressed.

The limitation of space in a clinic of this kind permits only the mention of two other cases which are illustrative of the main concepts of this clinic.

**Case IV.**—A young girl of twenty-five. Her chief complaint was that she blushed at inopportune moments, especially when the situation of itself contained no incident or occasion for blushing. When she felt the heat and saw the redness of her face in such moments she felt a sensation of weakness, confusion, could scarcely speak, felt foolish and powerless, and above all had the sensation that every one was observing her with not only curiosity but critically. This idea became so obsessive that she gave up a promising position for which she was carefully trained and entered a school for another kind of work, less to her liking and of a lower level of effort.

The neurological and physical examination of this young



woman was found to be within the normal other than a vasomotor instability of the skin over a large part of her body, and very marked unusual dermatographic responses.

An early sexual experience of an emotionally shocking character was regarded as the precipitating factor in conditioning the blushing response. Much further back in the patient's life were found many instances in which feelings of shame, guilt and sin resulted. The physical beauty of an elder sister as contrasted with her own unattractiveness made her very early self-conscious about her own appearance. Early defects in her teeth, which later were corrected, served to accentuate the feeling of her own physical self as an ever-present fact in her consciousness. The foundation of ideas of reference was thus early laid and the obsessive ideas associated with blushing and the beginnings of the ideas of persecution and of ill-defined delusions of a paranoid type developed inevitably from these early and at that time insignificant beginnings.

**Case V.**—The last case is one of recurrent depressive states in a young woman, a college graduate, trained as a teacher, and forced to give up active work by the constantly recurring depressed states. These produced a more or less constant state of a sense of growing incapacity and states in which confusion and a sense of unreality were becoming increasingly evident and constant. Associated with this was the usual emotional dulling repeated so often in the history of the early developing psychosis. The interesting point in this history is that at a very early age the patient had an attack of estivo-autumnal malaria, and it was for the treatment of this condition that her earliest medical contacts were made. Beneath and behind this actual organic disease was the growing environmental influence of a household disturbed by the conflict between a much beloved mother and a hard overdisciplined father. The death of the mother and a remarriage to a woman much inferior, socially and culturally, to say nothing of other qualities. An early step-mother situa-

tion in reference particularly to this girl. Years of extraordinary effort to attain the highest marks in school as a compensation for the unfairness and injustice at home. This effort was made in spite of the continuing periodic attacks of the malaria and against the periodic fatigue and ill-being characteristic of this disease.

It is clear again in such a case how definite is the opportunity of the practitioner to sense, to know and to identify the setting out of which the psychosis of later years developed.

These cases are picked at random representing only an insignificant percentage of possible material. Any general practitioner's practice is filled with like instances. For him is the opportunity for neuropsychiatric insight and opportunity for the prevention or alleviation of future neuropsychiatric diseases. There is no way of fulfilling the social obligations which his peculiar and traditional type of medical practice puts upon him other than to study not only sickness but the sick person. The purpose of this clinic was to point this out and the clinical sketches were devised to make this more realistic.

In conclusion the author feels that what he has said is what every general practitioner already knows—possibly better than he does.



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### THE DIAGNOSIS AND TREATMENT OF FUNCTIONAL DISORDERS OF CHILDREN

THE term "functional disorder" is attributed to those who show some type of physical disturbance, either subjective or objective, in whom no organic factors which could be held a responsible cause for the difficulty, can be demonstrated. Such manifestations are numerous and range from purely subjective complaints such as headache and abdominal pain, to the more definite physical disturbances such as enuresis, fecal incontinence, nausea and vomiting, stuttering, sleep disturbances, etc., and the more striking physical manifestations of various tics and hysterical paralyses.

The material on which this paper is based is taken largely from cases studied at the Child Guidance Clinic in St. Louis, a department of Children's Hospital, which has been in operation with its present personnel for eight years. Some 300 children have been seen annually for examination and treatment. These children, ranging in age from three to seventeen years, are of the so-called "normal" group, that is, the feeble-minded, epileptics, and those suffering from primary organic disease of the nervous system are excluded. They are referred to the clinic because they have become serious behavior problems at home, in school or in the community. While they are brought to the clinic primarily because of problems of behavior, approximately 40 per cent show some definite physical manifestations of nervousness. These include thumb-sucking, masturbation, hair-pulling, various tics, sleep disturbance, psychic vomiting, enuresis, fecal incontinence, stammering,

phobias, obsessions and hysterical reactions such as paralysis, fainting attacks, aphonias and blindness.

#### DIAGNOSIS OF FUNCTIONAL DISORDERS

The clinic study of problem children includes: (1) a study of the family background, medical and developmental history of the child, a long section picture in which heredity and environment are seen in relation to each other. (2) Psychological tests which give valuable information concerning the general level of mentality, specific handicaps, such as reading disabilities, and special abilities. (3) General physical examination and special examinations where indicated. (4) Neuropsychiatric study.

Investigation on this broad scope has shown significant relationships between emotional disturbances, behavior and functional disorders of decided value in the diagnosis and treatment of functional disorders. A brief survey of the nature of behavior, social as well as visceral, will assist in understanding this point.

All human beings are born with identical instinctive drives and emotional needs. Their primary instinctive drives are for self-preservation and for racial preservation or reproduction. Their primary emotional needs, which they constantly seek to satisfy are for security and social acceptance. While the instinctive drives and emotional needs of children are uniformly the same, the equipment which they possess and on which they depend to satisfy their needs show a remarkable degree of variation. That is, some inherit a pattern of growth which destines them to be feeble-minded while others possess the capacity for average or superior intellect. Others inherit a pattern of physical structure which places them at a serious disadvantage with their more vigorous associates. An equally great degree of variation probably exists in the less tangible but important factor which we may call emotional or nervous stability. Again there are those who, although potentially normal, from a hereditary point of view, suffer a degree of damage through trauma, infections and toxemias, which

seriously interferes with their development and impairs their ability to successfully meet life requirements.

Behavior is the physical manifestation of the individual's effort to satisfy its instinctive and emotional drives in whatever environment it finds itself. Its success in accomplishing this end depends on two factors: (a) its ability, physical and mental, and (b) the manner in which it has learned to use these abilities. The world is a competitive world and the child finds itself in a competitive position from an early age. It is only when the child finds itself subjected to a very severe shock, which seriously threatens its security, or to prolonged failure, that an emotional disturbance sufficient to produce a chronic behavior problem or a physical functional disorder, or both, results.

Seen from this point of view a functional disorder may then be considered as a symptom of increased nervous tension which in turn is the product of acute or chronic insecurity. The child's life can be divided, for purpose of study, into four main spheres: (a) home life, (b) scholastic life, (c) social and physical competitive life, and (d) sphere of physical growth and health. No child is or need be uniformly secure and successful in all these spheres but serious failure or fear of failure over a long period of time in one or more may be sufficient to produce decided emotional disturbance and a functional disorder. On the other hand those who are happy and reasonably secure and successful in these spheres do not suffer from functional disorders. This is an important point in the differential diagnosis of functional disorders. The whole developmental history of the child must be considered and it is extremely rare that functional disturbances develop in those who have made good adjustments in these spheres.

The more common causes of unsuccessful progress and disturbances of the child's emotional state may be summarized as follows:

- (1) In home sphere—(1) Broken homes, incompatibility and friction between parents. (2) Illness or death of parents.
- (3) Overanxiety and overprotection of the child by parents.

(4) Lack of affection and resentment of children because of poor ability. (5) Excessive partiality to other children and unfavorable comparison. A child subjected to any of the above situations for a relatively long period of time may develop not only a feeling of insecurity and resentment in relation to the home situation but carry over such feelings in its associations outside of the home, where they act as handicaps to his successful progress in group and school life.

(B) In the scholastic sphere—(1) Emotional disturbances and visceral disorders during the first few months of attendance at school are common. Sleep disturbance, enuresis and vomiting are the most common types of reactions observed. They occur particularly in cases of the only child who has been overprotected in its home and has had little opportunity for a normal competitive association with neighborhood children between the ages of three and five. The sudden transition from association with adults in the home to a strange school group is often sufficient to produce a marked degree of instability which in the majority of cases subsides in the course of a month or two. (2) Failure to progress in school work with subsequent criticism from teacher and home due to inferior mental ability, or frequent absences from school resulting from illnesses. (3) Failure to make normal scholastic progress as a result of special handicap in language work, *i. e.*, inability to learn to read or spell although general level of intelligence is normal. This type of difficulty manifests itself particularly in second, third and fourth grade and it occurs chiefly in those who show some evidence of lack of cerebral dominance or the so-called "inter-grade-handed" individuals. We have seen more than 300 cases of this type of handicap in the past five years and while this difficulty is due to a basic organic factor, the insecurity and emotional disturbances resulting from the persistent scholastic difficulty and failure frequently produce marked functional and visceral disorders. For example—a nine-year-old boy, who had shown increasing nervousness in the past two years, was examined at pediatric clinic. Infected tonsils

were found and tonsillectomy and adenectomy done. Patient made good recovery, but soon after return home developed a throat tic. He was then referred for psychiatric study where careful inquiry of life history showed he had made very satisfactory development until his second year in school, when he had increasing difficulty in his work and nervous manifestations soon followed and persisted. He had been placed on condition into third grade because of his good general ability, had failed in third grade work and was again doing failing work his second year in third grade when taken for medical examination. In spite of normal intelligence it was found that patient's reading and spelling ability were only at first grade level. He showed tendencies to reversal and other physical signs of intergrade handedness which clearly showed him to be a reading disability case. The mother was left-handed. Patient was put on program of remedial training, given an understanding of the nature of his difficulty and his nervous manifestations rapidly decreased. His tics returned two weeks before the end of the school year when he was told that although his work had improved a great deal, he was still unable to do satisfactory language work and it would be necessary to again repeat third grade.

A girl, age eleven, was admitted for study because of the development of attacks during which she suddenly stiffened out and slid from her seat to the floor, then assumed a tonic flexure attitude and emitted a peculiar whistling cry which continued at times for several minutes. The seizures, which had started two months prior to admission, at first occurred only at school, later occurred at home. Sleep was undisturbed, there was no actual loss of consciousness, no actual convulsive reactions and no after-period of headache or drowsiness. The girl was retarded in both physical and intellectual development, unattractive in appearance. Her parents were critical of her slow progress, made her do long periods of home work and she was unfavorably compared at school and home with her more capable brother and sister. She was in fourth grade in school, doing poor work and her nine-year-old sister was



doing good work in the same class. Earlier in the school year a classmate had suffered from convulsive seizures and was removed from school. The patient had witnessed several of these "shaking attacks" as she called them. Attacks quickly ceased while in the hospital but recurred when parents visited. Here the purpose, as well as the origin, of the functional disorder is obvious.

(C) The social and physical sphere—functional disorders primarily related to failure in this phase of development occur chiefly after ten years of age. The more common basic factors are (1) serious handicap in material or social advantages, especially among girls. (2) Inferior physical ability, especially among boys. (3) Special physical disabilities such as residuals of poliomyelitis, blindness, severe acne, etc.

A boy, age twelve, complained of attacks of gastro-intestinal pain, later phobias of being poisoned developed. For a month he had eaten only food which he took directly from freshly opened cans or which he bought in cellophane-wrapped packages at the store. He had been out of school for several months, sleep was badly disturbed and he had developed some facial tics. Physical status was essentially negative aside from a mild degree of malnutrition. History revealed that patient had been a nervous child from infancy on, had little opportunity for play with children, was popular and attractive to adults because of his intellectual precocity. He was of superior intellect, had been an outstanding scholar and until the past year had led his class. He was small, lightly built and had practically no knowledge of normal physical competitive skills, could not swim, had never played ball, marbles, skated and was extremely apprehensive of any physical combat. His keen intellect made him more sensitive to his inadequacies. This history survey resulted in the direction of treatment to an intensive physical development program rather than against his symptoms. He vigorously protested at first, but as skill and ability developed, interest followed, with most gratifying results.

(D) In the sphere of physical growth and health—handicaps of sufficient intensity to produce serious emotional and functional disorders fall chiefly in one of the three following groups.

1. Those whose patterns of physical growth have been such as to make them conspicuous and place them at a disadvantage in comparison with other children. In this group are found those who are unusually large or conspicuously small, those handicapped by physical malformations or deformities resulting from spastic plegias, infantile paralysis, etc., unusual rapidity or retardation in sexual development and marked adiposity. Any marked deviation may produce a degree of anxiety and introspection which seriously interferes with normal emotional health and successful adaptation.

2. Those who have been subjected to experiences of illness which has left chronic feeling of anxiety for their present and future health. Among this group cardiac cases are particularly prevalent.

3. Those who have become excessively introspective and apprehensive about their health, chiefly as a result of association with neurotic adults.

A ten-year-old girl was seen about a year ago because of persistent attacks of difficulty in breathing. She had been under treatment at pediatric clinic for some time. Complete physical examination including x-ray studies failed to show any physical causes for her difficulty. It was found that she lived alone with her mother who for years had suffered from poor health. The father had died some four years previously of tuberculosis. The child slept with the mother and the mother had so-called "spells" when she too had trouble getting her breath. The atmosphere of the home was drab. The child, although she had made normal school progress, had little opportunity for normal neighborhood play or physical activity because of her so-called "spells" and mother's anxiety about her health. She was subject to chronic sleep disturbance and frequently awakened at night in one of her difficult breathing attacks.

Another boy, age thirteen, suffered from enuresis, nightmares and occasional sleep-walking and attacks of palpitation. These symptoms developed after a medical examination two years earlier at which time he had been told by the doctor that he had leakage of the heart. He had been taken out of school, kept at home in bed for a period of a month and thereafter his physical activity had been sharply restricted. Patient had been out of school much of the time from that date and developed strong introspective tendencies and was in a chronically apprehensive, unhappy emotional state. It was found that patient's actual physical condition was such that he could well participate in normal physical activities. His response to a program which provided these together with measures to counteract sleep disturbance, enuresis and nervous tension was most gratifying.

#### TREATMENT OF FUNCTIONAL DISORDERS

The treatment of functional disturbances must be directed at: (a) the visceral disturbances or symptomatic level and (b) the correction of the basic causes responsible for the production of the emotional tension. No detailed discussion of treatment program for the wide variety of functional disturbances can be included in this paper. The important point of emphasis is that the visceral disorders be recognized as symptoms of an underlying difficulty so that treatment is not limited to the correction of the nervous manifestations. A few general principles should be kept in mind. (1) The patient has been subjected to emotional disturbances for a considerable period of time, nervous irritability is increased and consequently the intelligent use of sedative medication is extremely valuable, particularly in the earlier stages of treatment. This is especially true when as is often the case the emotional unrest continues through the night interfering with normal depth of sleep and interfering with the natural phase of rest and recuperation. (2) An attitude of sympathetic interest and inquiry beyond the physical complaints into the child's life at home, situation at school, opportunities and

interest in neighborhood associations, will do much to gain the confidence of the child and will also give the physician considerable information as to the sphere in which the child's security has been chiefly threatened. (3) Functional disorders are usually the result of a long period of emotional unrest, consequently their response to treatment is often slow. While the child should be assured as to the ability to cure the difficulty, the time element that may be required and the occurrence of occasional relapses should be frankly discussed with him. Too often the child is subjected to increased anxiety when treatment measures are not immediately or permanently successful.

Treatment measures directed to the basic causes must be determined by the factors revealed in the environmental study. In the case of the girl with the breathing difficulty, little could be done to change the neurotic nature of the mother, however, certain measures were outlined which at least diluted the intensity of the influence of the mother. It was insisted that patient must sleep alone and that she be provided with roller skates and spend at least one hour a day in out-of-door play. The mother accepted this on the basis of the child's need for fresh air and exercise. In addition to this it provided further separation from the mother and opportunity for play association with neighborhood children. In general it has been found that when parents realize the need of freedom from excessive criticism, approval for effort and the opportunity for association with other children, they will cooperate in planning to meet these needs. In a general way the same principle applies for assisting the child to overcome its handicaps in the other spheres of development—scholastic, physical and social. There are many cases in which the handicaps are of such a nature that they cannot be successfully overcome, such as seriously defective vision, defective intelligence, cardiac lesions, endocrine disturbance, etc. In such cases the problem lies in finding satisfying and constructive outlets to compensate for existing handicaps.



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### THE TREATMENT OF BRONCHIAL ASTHMA

As early as 1830, clinicians noted that paroxysms of bronchial asthma followed exposure to specific substances. No importance was attached to these observations until Meltzer,<sup>1</sup> in 1910, interpreted the asthmatic paroxysm as a phenomenon of anaphylaxis. As a result of observations in the clinic and in the experimental laboratory with this principle in mind, the therapeutic effectiveness in bronchial asthma has increased from 5 per cent to better than 50 per cent.

Since asthma means gasping, in the course of time it has been applied to a great number of diverse clinical conditions in which dyspnea is the presenting symptom. Such terms as cardiac, renal, thymic, and uremic asthma, and also asthmatic bronchitis have developed. Our present knowledge allows us to define bronchial, spasmodic, or allergic asthma as a recurrent paroxysmal dyspnea, particularly manifest in the expiratory phase, due to an allergic reaction in the bronchioles resulting from the absorption of a substance to which the individual is hypersensitive. This excludes those forms of dyspnea with wheezing breath sounds which mimic allergic asthma, such as, certain types of cardiac decompensation, bronchial stenosis from foreign bodies, or tumors, mediastinal and pulmonary disease. Neither wheezing breath sounds nor dyspnea connote hypersensitiveness. To avoid confusion, it would be desirable to indicate the clinical manifestation of hypersensitiveness as allergic asthma rather than the term

bronchial or spasmodic asthma by which most clinicians of the present day indicate these symptoms.

The mechanism of the attack has been a matter of controversy for many years. Bronchospasm has been considered the cause since earliest times and the discovery of the anaphylactic phenomenon emphasized this factor. Further support for the bronchospastic mechanism is had by the experimental data which indicates that bronchial constriction and probably secretion from the mucous glands can be initiated by stimulation of the vagus nerve. Edema, however, is the essential reaction in hay fever and vasomotor rhinitis, which is so frequently associated with asthma, and also in the allergic reaction in the skin, so that it seems logical to infer that edema of the bronchial wall may be the dominant cause. Further, this has been observed by bronchoscopic examination during asthmatic attacks and clinical experience with epinephrine supports the belief that edema rather than spasm is the dominant factor. In addition bronchial plugging with viscid exudate, which has some support by the appearance of the roentgenographic chest plate, with lipiodol visualization during an asthmatic paroxysm, must also be considered. Whether these reactions are brought about in all instances by central or peripheral stimulation of a circulating or contacting allergen, or by vagus stimulation, one or both, remains for further study to elucidate.

The clinical study of allergic asthma has established the following criteria for its recognition:<sup>2</sup> (1) There are allergic manifestations in the antecedents. (2) Other manifestations of allergy occur in the patient. (3) It usually starts in early life—the onset past the age of fifty is infrequent. (4) It is, in the beginning, chiefly paroxysmal in nature. Between attacks, for indefinite periods the patient is practically normal, presenting neither subjective nor objective symptoms or signs. As the condition progresses, attacks follow more rapidly, and complicating bronchitis and emphysema eliminate all free intervals. (5) Acute paroxysms are often preceded by symptoms of hypersensitiveness involving other systems, such as

hay fever, vasomotor rhinitis, gastro-intestinal disturbances, urticaria, and angioneurotic edema. (6) The most severe attacks occur while trying to sleep. (7) A tendency to periodicity in relation to the hour of the day or night, day of week, or season of the year. (8) Orthopnea is a prominent feature, even between paroxysms. (9) Emphysema is the usual finding; present at first only during the acute attacks, it later becomes a permanent feature. (10) Epinephrine will control the dyspnea in all except the most unusual instance. (11) Sputum collected during or shortly after an attack may show Curschmann's spirals, Charcot-Leyden crystals and almost invariably eosinophils. The coincident blood and sputum eosinophilia is almost pathognomonic. (12) The occurrence of positive skin tests. They are not the chief reliance of the etiologic diagnosis as allergic asthma may occur with negative skin tests.

There is no essential difference in the treatment of bronchial (allergic) asthma in the child from that in the adult. The fundamental requisite in either instance is the identification of the offending allergen, followed by its complete removal from the environment or the diet. There is no standardized treatment. The method of treatment is determined by the etiologic agents. One treats an individual and not a case of allergic asthma.

The treatment of allergic asthma resolves itself into the management of the asthmatic attack and the search for the fundamental cause. The treatment of the asthmatic attack can be undertaken without knowledge of its etiology, but the responsibility of the physician is not fulfilled with its control. All future endeavor should be directed toward the prevention of subsequent attacks.

The successful management of the acute severe paroxysm of allergic asthma is dependent upon the subcutaneous use of epinephrine hydrochloride 1:1000, probably better known as adrenalin. Except in those who have developed a tolerance for it, doses up to 0.3 cc. are as effective as larger ones, without the unpleasant and sometimes alarming side actions of the larger doses. A satisfactory method of using the drug is



to fill the syringe with 0.5 cc. more or less, and with the syringe remaining in place, to inject 1 minim or 0.1 cc. a minute until the attack begins to subside or until beginning physiological effect is noted by pallor, which is often first seen about the nose by tangential light, by fibrillary muscle tremor, or by palpitation. When physiological effect is obtained, there is no need to administer more epinephrine even if there has been no improvement in the attack. In an emergency, however, one need not be concerned with overdosing, and enough should be given to produce the desired effect. In some instances of status asthmaticus, it has been possible to give several cubic centimeters of adrenalin by the slow continuous subcutaneous administration without inducing side effects.

Ephedrine and the oral inhalation of adrenalin 1:100 solution by means of an all-glass nebulizer producing a very fine spray, are useful only for mild attacks; attacks which are more a discomfort than a paroxysm of bronchospasm. In children, the cough is readily controlled by codeine when mere change of environment or avoidance of specific foods plus subcutaneous adrenalin is not entirely effective.

The management of the frequently repeated paroxysm of allergic asthma revolves about the search for the causative agent, the administration of adrenalin and sedatives and maintaining the nutritional state, until the etiological factor is found. The prolonged or continuous attack is often benefited by change to an environment where all the usual causative allergens are absent. Experience has shown that admittance to a hospital in which the usual extrinsic causes (feathers, orris root, wool, cotton seed, insecticides, animal pets, house dust) are avoided brings about cessation of attacks within five days. This, in itself, is diagnostic and points to an environmental factor as the cause. Some cases require, in addition, short periods of starvation or some type of elimination diet before relief is obtained. In these instances, one assumes that an ingestant may be an added etiologic factor.

When dietary manipulations and environmental change aided by the subcutaneous administration of adrenalin do not

about a cessation of the paroxysms, sedatives are necessary. They are of particular benefit when there is extreme pulmonary dilatation as shown by great hyperresonance at the apex and absence of downward expansion of the lungs by percussion. In these instances the slightest exertion, eating, talking, or cough increases the already existing discomfort. The effect of epinephrine becomes transitory even with increasing dosage and shorter intervals of administration. The therapeutic indication is absolute rest and control of the

When cough is not a prominent part of the symptomatology, sedatives of the hypnotic series are helpful when given solely for their physiological effect, provided there is no sensitization to the drug. When the pulmonary dilatation is accompanied by frequent cough, morphine or pantopon is useful in repeated doses, provided no idiosyncrasy exists. *These drugs never be given in the customary dose of 0.015 Gm. ( $\frac{1}{4}$  grain), or 0.01 Gm. ( $\frac{1}{6}$  grain) respectively.* When employing these drugs the respiratory rate must not decrease below 20 per cent, and a fluid intake of 3000 cc. for twenty-four hours must be maintained (sputum cannot liquefy in a dehydrated patient). For the adult, a satisfactory method is to give morphine 0.004 Gm. ( $\frac{1}{16}$  grain), or 0.005 Gm. ( $\frac{1}{12}$  grain) hypodermically. If the cough or restlessness is not allayed after several injections at three- to four-hour intervals, the dose may be cautiously increased to 0.008 Gm. ( $\frac{1}{8}$  grain), or 0.01 Gm. ( $\frac{1}{6}$  grain)—but never at any time allowing the respiratory rate to fall below 20 per minute or the patient to become more than lightly narcotized. It is unusual to require more than 0.015 Gm. ( $\frac{1}{4}$  grain) morphine, or 0.01 Gm. ( $\frac{1}{6}$  grain) pantopon during the twenty-four hours. In some, better results are obtained by combining the morphine or pantopon with small doses of adrenalin. This condition also requires individualization of treatment. With the administration of morphine, glucose solution should be given orally and normal saline solution subcutaneously to the patient. Adrenalin (5 to 1000 cc.) can be advantageously

added. The amount of fluids given should be governed by the degree of dehydration. Coexisting abdominal distention should be relieved by enemata as soon as the condition of the patient permits, and a small catheter left in the rectum to allow of the easy expulsion of gas.

Many variants<sup>3</sup> of the therapeutics for this clinical phase of allergic asthma are proposed by clinicians with extensive experience in the care of these cases. These will be found satisfactory for selected cases. As yet no one method is applicable in all instances. They usually concern the type, dosage, and technical administration of their favorite sedatives, and the simultaneous management of the associated dehydration and nutritional state.

Treatment of the allergic state responsible for the acute paroxysm requires a study of the patient as a whole, considering his heredity, the environment and the peculiarities, and the dietary habits, correcting abnormalities as found by physical and laboratory examinations and the interpretation of observed reactions. One needs not only a thorough knowledge of internal medicine and its diagnostic handmaiden allergy, but also an expanding experience with allergic patients and their psychology. When one knows the allergic cause of the acute paroxysm it is easy to explain the bizarre and extraordinary circumstances under which they occur. Absolute and complete avoidance of the offending substances, whether inhalant or ingestant, is all that is necessary to bring about a clinical cure. If the substance cannot be avoided, benefit will be obtained in a certain percentage of cases by hyposensitization. If the asthma has induced incapacitating chronic pulmonary emphysema, or chronic bronchitis, or purulent sinusitis, appropriate therapeutics may be needed for these. The best prophylactic treatment is the recognition of the allergic manifestations during childhood, thereby preventing the chronically ill adult with the inevitable sequelae of frequently repeated asthmatic attacks.

In this presentation we shall limit ourselves to a discussion of the treatment of patients with allergic asthma in whom

specific treatment was of benefit. It can be readily seen that without the advantage of the knowledge gleaned from clinical observations and sensitization tests these patients undoubtedly would have had a long-standing chronic illness and that they also may have had improvement seemingly coincident with certain therapeutic measures, but actually due to the unwitting avoidance of the causative agent.

It is possible to present before you a group of patients upon whom we have information extending over many years. The knowledge of their etiologic factor makes their seemingly erratic course not surprising, and helps to explain the clinical course of other asthmatics. They make one acutely aware that in bronchial asthma, the factor of coincidence will credit many diverse therapeutic measures, either of the past or contemplated, as cures, when in reality it was the unknowing avoidance of the causative agent which initiated the cure. As an example (which appears in many different forms in one's experience with allergic individuals), there is the business man of forty-six years of age, who sought relief for his nonseasonal asthma of several years' standing, which was a recurrence of nonseasonal asthma he had had from early childhood to the age of twenty years. At that age, he came from the farm to the city and coincidentally had a nasal operation. In the course of time while living in the city his asthma disappeared. He was sensitive to horse dander, which undoubtedly accounted for his early asthma as it did for his present asthma because he had taken up horseback riding. The operation had been credited with the cure and not the unconscious avoidance of horse contact. It is interesting to speculate in those instances in our experience where the offending substance was deliberately avoided, as to what would have been credited with the cure had the same avoidance occurred unwittingly.

**Case I.**—The first patient I wish to present is a forty-five-year-old married woman, who was seen for the first time in 1919. At that time she was the subject of nonseasonal asthma since the age of four, and change of weather was thought to

precipitate the attacks. During her high school years she most frequently had an attack on Saturday evenings and Sundays. During the first year of her college education she had many severe paroxysms. During the ensuing vacation from college, a nasal operation was performed and the next year at college, there was improvement, attributed to the operation, in that the attacks were less frequent but no less severe. During her third year at college she again had frequent severe paroxysms. After her graduation, she spent time in various portions of the West where the attacks were also less frequent but still quite severe. In the later years of her complaint, she noticed that wheat flour produced the hay fever syndrome but was not certain that it induced the asthmatic attacks. It was in 1919 that she was found sensitive by skin tests to the proteins of wheat flour, and since that time has been free from asthmatic attacks except at those times when she has either willingly or unknowingly had contact with wheat. We are now able to explain the apparent vagaries of the disease during the early years. The asthmatic attacks on Saturdays and Sundays were due to helping with the baking, which was done on Saturdays. The Sunday asthma was due either to the tapering off of the asthma initiated by contact with wheat flour on Saturday or to the ingestion of the products baked on that day; for later observation showed that the asthma could be precipitated either by inhalation or ingestion. The severity of the first year at college was due to the fact that her course of study required the handling of wheat flour. The improvement during the second year, credited to the nasal operation, was due to not handling wheat flour during this year, the only contact being by ingestion; during the third year, flour again was handled accounting for the increase of paroxysms. She was treated by oral hyposensitization with wheat, beginning with minute quantities of wheat bread, increasing the dose every five days so that at the end of nine months, she was able to eat a satisfying quantity of wheat products. During this period and ever since, the inhalation of wheat flour has always been followed by hay fever-like symptoms and if sufficient

quantity were inhaled, by bronchospasm. In the beginning a gauze mask covering the nose and the mouth, and later a wet sponge respirator prevented these symptoms whenever handling flour.

In 1926 her thyroid was removed for hyperthyroidism. There had been no asthma. The first recurrence of frequent severe asthmatic attacks occurred in 1930 despite sedulous avoidance of contact with wheat flour, both by inhalation and ingestion. This asthma occurred in a town to which she had moved some three years previously and which contained both a flour mill and a grain elevator. She gave positive skin tests to the dust from the flour mill and from the elevator, as well as to the original wheat proteins. Moving to a town 5 miles away, containing neither a flour mill nor a grain elevator, again cured her of the asthmatic paroxysms. Had we not known of her sensitization to wheat, the elucidation of these attacks would have been a great deal more difficult. Indeed they were attributed to bacterial sensitization by the home physician. At the present time, she is free of asthma as long as she avoids inhalant contact with flour. She can again eat satisfying amounts of wheat flour products, without having had oral hyposensitization.

**Case II.**—The next patient is a man now forty-five years of age, who was first seen in November, 1916, at the age of twenty-five years, complaining of asthma which began at the age of sixteen years, having had a gradual onset with much coryza and cough. The attacks occurred usually in the middle of the night, and were worse in winter; the previous summer having been the first time he was troubled during the summer season. He had had the tonsils, adenoids, and turbinates removed, and the nasal septum straightened without effect upon his asthma. The past medical history had no bearing on his present trouble, except that he believed his attacks were initiated by colds, sudden chilling, drafts, or walking in the park. The physical examination showed a spare, fairly developed white male, weighing  $118\frac{1}{2}$  pounds, with a

chief physical finding of expiratory musical râles diffusely scattered over his chest. The x-ray of his chest showed considerable generalized branching, dense hilus shadows on both sides extending to the bases. On November 8, 1916, he was placed upon a high caloric diet and started on injections of autogenous defibrinated blood. By January 6, 1917, he had received 8 injections of defibrinated blood in increasing doses and had gained 18 pounds in weight, but had had two severe and five light attacks of asthma. Although the gain in weight was most striking and probably beneficial and occupied the foreground of his therapeutic picture, the effect upon his asthma either of the injections of autogenous defibrinated blood, or the high caloric diet were not so striking. On this same diet he reached his best weight on March 19, 1917, weighing 145½ pounds.

He had attacks at irregular intervals averaging one attack in two weeks, some characterized as severe, others as light, until January, 1917, when they increased in severity and frequency. He received another series of defibrinated blood injections in increasing amounts, this time without specific dietary instructions. During this series, his weight decreased from 142 pounds to 124 pounds with no notable change in the frequency or severity of his attacks. Both severe and light attacks continued at about two-week intervals, and another series of defibrinated blood injections were given during 1918; again without notable influence upon his dyspnea. In 1919, he was found sensitive to wheat by the cut method.

By avoiding wheat he has remained free of asthma and the frequent so-called "colds" until August 29, 1925, when it recurred despite complete wheat avoidance. There was an associated coryza of moderate severity but no itching of the inner canthi or nose, which made pollen doubtful as the cause, and intracutaneous tests with 1:10 ragweed solution were negative. A positive intracutaneous test was obtained to corn, which elicited the information that he had been eating a great deal of popcorn. The attacks ceased when he stopped eating popcorn; but that is not the whole story. Corn meal had been

used since 1919 as a substitute for wheat flour, and he had eaten as much corn on the cob as he wanted without asthma following so that the popcorn was a specific sensitization and one assumes the other forms of corn induced no symptoms because in their preparation for the table they were exposed a longer time to heat. At least by avoiding wheat and popcorn, but eating corn in other forms, he remained free of asthma.

In 1931 he experienced a nasal infection, without asthma, necessitating irrigation of the left antrum with recovery of purulent secretion.

In early September, 1932, he again had a recurrence of asthma with coryza without itching of the inner canthi and nose. Intracutaneous tests with ragweed were negative, and positive reactions were obtained to cantaloupe, spices, chocolate, and nuts. Cantaloupe with black pepper had been eaten frequently during the previous ten days. The asthma ceased when they were omitted from the diet. He is still free of asthma by omitting from the diet wheat, popcorn, melons, chocolate and nuts.

**Case III.**—This patient was seen for the first time in 1921 at the age of five years, complaining of frequent colds and asthma, which he had on the average of one time a month since the age of one year. He had had eczema beginning at six weeks which lasted until about the eighth month and shortly thereafter the asthma began. He was a nursling, and the eczema disappeared when breast feedings were stopped which was coincident with the use of a new salve, which was credited with the cure but which I am inclined to believe was due to an entirely different cause. From the diagnostic standpoint, the important fact in the history of this eczema during the nursing period, was that the mother took a malt preparation to improve the quality of the milk; for skin tests were positive to wheat, egg, and potato. The asthma was completely controlled by avoidance of these foods. A fair tolerance to wheat



was obtained by oral hyposensitization and the other offending foods were gradually added to the diet.

He was seen again in 1927 because of abdominal pain which simulated appendiceal involvement. Because of the absence of the classical associated symptoms and laboratory findings, and the history of excess indulgence in wheat and egg, it was postulated that the pain was due to allergic involvement of the intestines. A subsequent attack of abdominal pain was accompanied by blue spots on the lower extremities so that the diagnosis of Henoch's purpura seemed clear. Positive reactions to wheat, egg, and potato were again obtained and when these foods were deliberately eaten, acute abdominal pain and purpuric blotches on both legs occurred within a few hours.

Another course of oral hyposensitization allowed the ingestion of adequate amounts of these foods without inducing symptoms.

Being imbued with the carefree spirit of youth, the adherence to a diet is somewhat onerous so that he has been seen from time to time since 1927 with either mild asthma or abdominal pain, always traceable to excessive indulgence in the proscribed foods. Since 1934, he has had mild hay fever like symptoms without notable itching, corresponding to the pollenating periods of the grasses and ragweed. Cutaneous reactions are positive now to the pollen of oak, timothy, and ragweed, and still to wheat, egg, and potato. Hyposensitization to these pollens has not been attempted because of the possibility of these symptoms being controlled by strict avoidance of the known offending foods, particularly so since itching of the inner canthi and nose is not present.

**Case IV.**—The next patient now twenty years of age was seen in the dermatologic clinic at the age of seven months in 1917, with a vesicular papular dermatitis of the cheeks which improved with medication by late spring. She was seen again in the dermatologic clinic in 1919 and 1921 with similar dermatitis, which at the last visit involved the face, arms, wrists,

elbow folds, back, and chest. Each time the dermatitis disappeared with the onset of warm weather. She was seen next in the asthma clinic in 1925, having had nonseasonal asthma with exacerbations in the spring and fall for two years. Since the advent of the asthma, there had been no dermatitis. She gave positive reactions to feathers, wool, dog, ragweed pollen, potato, and milk. She avoided contact with these and was given prophylactic injections of ragweed pollen for two seasons. There has been neither asthma nor dermatitis since 1925.

**Case V.**—A woman, now twenty-four years of age, was first seen at the age of ten years in 1922. At that time she had had persistent head colds with nonseasonal paroxysmal sneezing and nonseasonal asthma for two years. Most thorough rhinological operations and treatment had influenced the course of her complaint only temporarily. Positive skin tests were not obtained. She always became promptly free of her asthma with hospitalization, and it disappeared completely when she left home at the age of eighteen years, and has not recurred up to the present time. Because of the symptomatic history, the age of onset, and the prompt disappearance of asthma with each hospitalization, she was considered as having allergic asthma. Undoubtedly she was sensitive to an environmental factor, which we were unable to identify.

These patients can now experience the various circumstances, which were thought to cause their attacks. They also illustrate very well the clinical mutations of allergic individuals. Despite the clinical dissimilarities occurring during the course of their affliction, it is obvious that the treatment is the same irrespective of the phase for, or the age at which medical aid is sought. However, they are cured only in the clinical sense. Immunologically they are not cured as evidenced by the persisting cutaneous reaction, by their ability to develop new sensitizations, and by the recurrence of symptoms upon exposure to a sufficient amount of the offending agent.

The clinical experience with them warns us to beware of drawing hasty favorable conclusions from the results of therapeutic procedures. Time is the determinant of the value of therapeutic measures in allergic asthma.

The following cases illustrate some of the methods of interrogation and of treatment.

**Case VI.**—This young girl is now thirteen years of age and was seen for the first time in October, 1935. She had had nonseasonal asthma since the age of three years, with one week as the longest period free of her discomfort. She also sneezed excessively the year around. She was worse in damp weather. She has had no other allergic manifestations. She sleeps in a feather bed, uses feather pillows; there is a canary bird in the house; the father handles horses; she lives within two blocks of a feed store and there is a grain elevator 8 or 9 blocks away. It is thought that certain foods and odorous substances increase the severity of the asthma. There is a positive family history for allergic manifestations, in that the maternal grandfather had asthma all his life; the maternal grandmother and the mother had and have sick headaches.

When first seen she weighed 65 pounds. She was pale, had flabby muscles, and a dorsal kyphosis of moderate angulation. The lungs were hyperresonant and had lessened downward expansion. There was no wheezing. The heart was normal. Intracutaneous tests resulted only in suggestively positive reactions to all inhalants, with the larger reactions to house dust and horse dander, and to cotton seed, corn, pea, lima beans, and spices.

Fortunately, while in St. Louis, she lived with a family who practiced "allergic cleanliness,"<sup>4</sup> the method necessary to avoid contact with inhalants. She became free of asthmatic attacks and, in addition, learned by example the manner in which asthmatics cooperate with their physician. She was under active observation for three weeks during which time she had one mild attack following a visit to a beauty parlor to have her hair set. Comfort was obtained by the oral use

of ephedrine 0.025 Gm. and further attacks from this source prevented by immediately thoroughly washing the hair. A high caloric, high vitamin diet was prescribed in the beginning, excluding only the foods giving suspiciously positive reactions. With the exception of cotton seed and spices, which are unimportant dietary constituents, the suspiciously reacting foods were fed deliberately. None of them induced symptoms, so that finally she ate a general diet, excluding cotton seed and spices, with special stress upon vitamin and mineral-containing foods.

At the end of our active observation she had gained 13 pounds, had better color, felt stronger and had experienced the longest period free of asthma in her life.

The skin tests are of no help in this case in identifying the specific etiologic agent, nevertheless the treatment should be along allergic lines since the clinical history and course is that of an allergic individual with allergic manifestations in her antecedents.

The clinical course points to an environmental and not a dietary factor, so that the therapy must be directed toward avoiding those present in her home environment, which were not present in the environment while living in St. Louis.

Accordingly, before she went home, the parents were sent ahead to duplicate the St. Louis environment, namely: no feathers, wool, cotton seed, house pets, orris root, and insecticides. She was instructed to avoid contact with animals, the feed store, and the grain elevator. It was explained that even under these circumstances, going home was an experimental observation. A diary was to be kept, noting all activities and all food ingested so that if the asthma recurred one knew accurately of the attending circumstances. The diet was to be similar to the one she ate while in St. Louis. Gymnastic exercises were prescribed in the hope of straightening her back. She has had no asthma up to the present time. She has not missed a day at school (and it has been a severe winter) and she weighs  $87\frac{1}{2}$  pounds, a gain of 22 pounds.

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The clinical course points to an environmental and not a dietary factor, so that the therapy must be directed toward avoiding those present in her home environment, which were not present in the environment while living in St. Louis.

Accordingly, before she went home, the parents were sent ahead to duplicate the St. Louis environment, namely: no feathers, wool, cotton seed, house pets, orris root, and insecticides. She was instructed to avoid contact with animals, the feed store, and the grain elevator. It was explained that even under these circumstances, going home was an experimental observation. A diary was to be kept, noting all activities and all food ingested so that if the asthma recurred one knew accurately of the attending circumstances. The diet was to be similar to the one she ate while in St. Louis. Gymnastic exercises were prescribed in the hope of straightening her back. She has had no asthma up to the present time. She has not missed a day at school (and it has been a severe winter) and she weighs  $87\frac{1}{2}$  pounds, a gain of 22 pounds.

**Case VII.**—The next lad was first seen at the age of four years, in December, 1930, accompanied by overly solicitous and unduly alarmed parents (the mother reeked with the odor of orris root). At the time he had constant nonproductive cough and wheezy breathing which had been present for some eighteen hours and he reflected his parents' state of mind by extreme irritability and unmanageableness. It was impossible to obtain a coherent clinical history, and physical examination revealed no fever, dry pharynx without exudate, hyperresonant chest with diffusely distributed short inspiratory and expiratory wheezing. Control of the cough and pacification of the parents was the therapeutic goal. Accordingly, absolute bed rest and enforced quietness; 0.015 Gm. of codeine every three hours, steam inhalation, avoidance of orris root, feathers, wool, and copious fluids were prescribed. The cough and wheezing subsided within twenty-four hours, and the child was without symptoms in five days. It was now possible to ascertain that his mother, maternal grandfather, and a maternal aunt had migraine; that another maternal aunt and a maternal great-aunt had seasonal hay fever, and that the father had sinus headaches of undetermined etiology; that the patient is subject to colds, which consist of nonseasonal paroxysmal sneezing, with itching of the nose for periods of twenty-four hours; that he sneezes upon the slightest provocation; that the ingestion of chocolate is followed by vomiting; that he had a constant nonproductive cough last year and an exactly similar ailment, which resembled pertussis, the past summer; that he has had diffuse urticaria of unknown causation one time; that he has recurring perianal dermatitis, and that he had more paroxysmal sneezing the past August and September. The clinical history is that of an allergic individual.

Feathers, pyrethrum, wool, orris root, cotton seed, kapok, flaxseed, the pollen of box elder, timothy, ragweed, and marsh elder among the inhalants; radish, turnip, sardine, almond, peach, and hazelnut among the foods, gave definitely positive reactions. Suggestively positive (erythema without whealing)

reactions were obtained to wheat leucosin, bran, buckwheat, casein, coffee, string beans, and tomato, by the cut method.

As the result of these preliminary observations the parents were advised the following basic regimen: (1) Complete and sedulous avoidance of contact with pyrethrum, feathers, orris root, cotton seed, kapok, flaxseed, and wool. This necessitated a change to nonorris root containing cosmetics and powders; getting rid of overstuffed furniture, and all feather pillows; encasing the mattress with a material impervious to dust; discontinuing the use of insecticides, and the substitution of cotton for wool blankets. (2) The clinical history pointed to the recent exacerbation of nasal symptoms during August and September, so hyposensitization injections to ragweed were begun. The clinical significance of the cutaneous reactions to the pollen of box elder and timothy to be determined by the correlation of observed symptoms to their respective pollenating periods and hyposensitization injections to be instituted to these, if indicated, the following year. (3) Avoidance of the foods (including cotton seed) giving definitely positive reactions. The dietetic diary to determine the clinical significance of the foods giving suspiciously positive reactions and of foods which gave no cutaneous reaction and also to determine the unknowing use of the prohibited foods. (4) Ephedrine hydrochloride in 3 per cent solution, dose 5 to 20 drops, to control audible wheezing, and  $\frac{1}{4}$  grain of codeine to control excessive cough was prescribed.

The period of observation was also utilized to impress the parents that their oversolicitude and evident alarm had a deleterious influence upon their child. Children with asthma should lead a normal existence, should indulge in the ordinary and usual activities of children. The only restrictions placed upon them relative to their affliction, should be the absolute prohibition of those substances proved by clinical trial to induce their attacks. As a matter of fact, when children learn that certain substances induce their asthma, they are more cooperative than adults.

During the subsequent years he was observed with small



amounts of dermatitis in the elbow and knee folds which appeared to follow the ingestion of orange juice. Chocolate, egg, chicken, and wheat induced vasomotor rhinitis. The most severe attack of asthma under observation developed in 1932, the first night he slept on a newly purchased day bed, which was said to contain no cotton seed because the label stated it was made from "pure cotton linters." An exactly similar episode occurred a year later while visiting in another city.

Transient and mild nasal symptoms developed during the pollenating periods of box elder and timothy. He was given prophylactic hyposensitization injections to ragweed for three sequential years. The first year he had moderately severe nasal symptoms without asthma. These were alleviated by avoiding chocolate, chicken, egg, and wheat in the diet and staying indoors in a closed room during periods of greater severity. The second and third years, he had only occasional nasal symptoms, not requiring pollen precautions, by avoiding the same foods. No ragweed hyposensitization injections have been given since 1933. There has been no asthma but he still avoids the inhalant allergen. The previously implicated foods are only strictly avoided during the ragweed season, during which time he has no more than a wet nose. As yet no symptoms are present during the period of timothy or box elder pollination.

He has grown and developed satisfactorily and his back is straight. As you will recall the previous case had a kyphosis as the result of constant asthma beginning about the same age as in this boy. He had the potentiality of developing the same deformity. The clinical course points to cotton seed as the dominant cause of his allergic asthma.

Although it is unusual for allergy to induce active symptomatology in those of advanced years, nevertheless by applying the criteria for its recognition to those past the fifth decade, one may identify some of these senescent complaints as being allergic in nature. The following two cases are examples of allergic asthma in those of advanced years.

**Case VIII.**—This woman was seen for the first time in early 1934, at the age of sixty-one years. She complained of sneezing, coryza, and cough leading to chest oppression with wheezy breathing of such severity as to require epinephrine for relief since November, 1933. Six years previously she had had similar chest oppression, often with head colds, for a period of two years. She also has, for the past several years, dyspnea without wheezy breathing upon moderate exertion.

Up to six years ago she had been in excellent health, living and working upon a farm as well as rearing ten children. There have been no physical ailments suggestive of hypersensitiveness up to that time. Since, hives occurred one time following a hypodermic injection to relieve an asthmatic attack; another time she has had edema of the lips and cheeks suggestive of angio-edema; during the past two winters, she has had frequent and nearly continuous head colds characterized by nonpurulent nasal discharge, intranasal blocking and without fever; aspirin is followed by a burning sensation in the epigastrium and a smothering feeling but never a definite asthmatic seizure. No history can be elicited of allergic manifestations in her antecedents.

The onset of her presumed allergic symptoms is not concurrent with any change in her environment. Feather pillows and wool comforts are used for bedding, and cattle, chickens, and cats are close by her house.

Essentially, on physical examination, are mildly cyanotic lips, a heart rate of 100 beats per minute, the second aortic and pulmonic sounds are of equal intensity, no wheezing breath sounds, three fingerbreadths and two fingerbreadths downward expansion of the right and of the left lung respectively; blood pressure, 140/90; fixed kyphoscoliosis, and uniformly thickened brachial arteries. A moderate number of eosinophils were found in the sputum.

The immediate therapeutic need was to lessen the cough, which was accomplished with codeine. Definitely positive reactions to the pollen of oak and ragweed were obtained by the intracutaneous method. The remainder of the inhalants

while not giving unmistakably positive reactions always produced larger intracutaneous responses than the foods, with the exception of spinach, turnip, lettuce, asparagus, corn, beans, cantaloupe, cabbage, and sweet potato. Accordingly she was advised to get rid of all the feathers in the house, the wool comfort, to stay out of the chicken house and the barn.

With adherence to these instructions, within a month there was lessening of the frequency and intensity of the chest oppression. Since that time she has had no dyspnea. During the latter part of August, there was a mild vasomotor rhinitis, probably due to the pollen of ragweed. It required no specific treatment. No symptoms developed during the period of oak pollination. Hyposensitization to these pollen is not indicated until symptoms of incapacitating intensity develop when these pollen are in the air.

**Case IX.**—This patient was seen for the first time in 1926, at the age of sixty-eight years, complaining of nonseasonal asthma over a period of thirty-five years. She had frequent head colds (afebrile, stuffiness in the nose with nonpurulent discharge) during the winter and was an easy sneezer at all times. There was no distinct seasonal variation of the intensity or frequency of the sneezing. She had been in excellent health otherwise. She had had no other allergic manifestations nor were there such in her antecedents.

The essential points in the physical examination were a moderate pulmonary emphysema and overweight. Both the sputum and the nasal secretion contained many eosinophils. Intracutaneous tests were positive to feathers, orris root, wool, and horse dander in equal intensity among the inhalants; and tomato, potato, black pepper, and string beans among the foods.

She remained under observation two months without notable improvement because, as later observation showed, she was not convinced that her "nice feathers" which had been in the family for two generations "could give her asthma."

She was next seen in early 1935 at the age of seventy-

seven years, because she was no longer obtaining relief from the patent nasal spray and patent medicines. The physical examination revealed short inspiratory and expiratory wheezing diffusely distributed over the chest cage in the sitting posture, no downward expansion of the lungs, and moderate cyanosis of the lips and nail beds. The recumbent posture quickly intensified her discomfort and the sitting posture was made more comfortable by many large feather pillows. She was placed in the hospital where she completely avoided feathers, wool, and orris root, and foods eliminated from her diet as indicated either by intracutaneous tests or the dietetic diary. She became free of asthma in seven days. At this observation, she gave intracutaneous reactions to milk, pepper, tea, banana, and spices among the foods, and feathers, wool, pyrethrum, and orris root among the inhalants.

This experience was sufficiently impressive so that she willingly duplicated the hospital environment in her home. As the result, she now has been free of asthma and head colds for a longer period than any time during the past forty-six years. The foods giving positive reactions have been added without inducing any symptoms so that the "nice feathers" probably were the dominant cause of her discomfort.

#### SUMMARY

Epinephrine, hypodermically, is the sole drug to be used to relieve the acute asthmatic paroxysm. In one unaccustomed to its use, 0.3 cc. is usually sufficient. When the attack is continuous, sedation is necessary and often life-saving, especially when extreme pulmonary dilatation exists. Oxygen is helpful when more than a mild degree of cyanosis exists. The oral use of ephedrine is efficient only for mild attacks. The prolonged or continuous attack is often benefited by change to an environment where all the usual offending allergen are absent. Occasionally such attacks are also mitigated by a short period of starvation or by elimination diets. During all attacks the patient should be kept in a warm room and bodily warmth maintained.

Paroxysms of bronchial asthma are prevented by completely avoiding contact with the offending substance and all other factors which act as secondary stimuli. The principal reason for therapeutic failure is the superficial and incomplete instructions to the patient as to the manner in which he obtains contact with offending substance and the means he must employ to rid himself of that contact.

Hyposensitization should be employed when it is impossible to avoid the offending allergens. For the foods, this is best accomplished by the oral route, beginning with infinitesimal amounts and increasing the dose until normal amounts can be taken. For the inhalants, the method is identical with the methods used for the treatment of hay fever with pollen solutions.

The best therapeutic results in bronchial asthma are obtained by: a study of the patient as a whole, considering his heredity, his environment, and his peculiarities; correcting the abnormalities found by physical and laboratory examinations; evaluating the influence of controlled environments; interpreting the observed reactions resulting from cutaneous testing, ingestion of foods, and administration of drugs in the light of past experiences, and the application of treatment guided by the integration of this knowledge.

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## CLINIC OF DR. ALEXIS F. HARTMANN

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### VOMITING IN THE NEWBORN

THE occurrence of vomiting in the newborn or young infant demands prompt investigation. While it may prove of little significance in a majority of cases, neglect of it in others may lead to serious results in a number of ways: (1) aspiration into the lower respiratory tract may result in asphyxia or fatal infection; (2) the *causative* factor may escape early detection and progress to a degree dangerous to life; or, (3) the resultant intake of food and water may be so reduced as to lead to severe degrees of malnutrition, dehydration, and chemical changes in the body fluids.

The most frequent causes for vomiting in the young infant may be classified for purposes of discussion as follows:

- I. Improper food or technic of feeding:
  - (A) Too much swallowed air.
  - (B) Too much food.
  - (C) Too frequent feedings.
  - (D) Unsuitable composition of food.
- II. Obstruction in the gastro-intestinal tract:
  - (A) Esophageal.
  - (B) Pyloric.
  - (C) Duodenal.
  - (D) Anal.
- III. Infection:
  - (A) Enteral.
  - (B) Parenteral.
- IV. Derangement of central nervous system:
  - (A) Intracranial conditions.
  - (B) "Autonomic imbalance."
  - (C) Habit.



## I. IMPROPER FOOD OR TECHNIC OF FEEDING

(A) **Too Much Swallowed Air.**—Air seems always to be swallowed during the act of nursing. Undoubtedly, however, some infants tend to swallow much more air than others, and these may be either breast-fed or bottle-fed infants. Inverted or poorly developed nipples and an insufficient milk supply seem to be the chief reasons for swallowing too much air in the case of the breast-fed infant. In the case of the bottle-fed infant, nursing in the supine position, especially when nipples with improper-sized holes are used, usually accounts for the difficulty in the bottle-fed baby. Improvement usually follows correction of these factors, particularly if the infant is made to belch once or twice during the feeding and again at its end. Belching, of course, should be done in the upright position. It is surprising, however, how difficult it is to hold a very young infant properly on one's shoulder when he insists on keeping his thighs sharply flexed on his abdomen, but in other respects acts more like a jellyfish. In such infants more favorable results may frequently be obtained by holding him in the sitting position on one's lap, or balancing him, face downward with his abdomen on the palm of one's hand.

(B) **Too Much Food.**—Vomiting following the ingestion of too much food is more likely to be seen in the bottle-fed than the breast-fed infant, because of the fact that too dilute formulae are apt to be offered the former, necessitating a large volume to provide adequate caloric intake. When the caloric value of the feeding averages about 20 calories per ounce (as is true of normal human milk) it is unusual to see healthy infants incapable of taking and retaining sufficient quantities to meet their caloric needs. This happens fairly commonly, however, in premature babies, and somewhat less frequently in undersized infants, especially when handicapped by serious constitutional abnormalities.

(C) **Too Frequent Feedings.**—Vomiting of some degree,

which may be no more than a small amount of "regurgitation," is, as a rule, seen in infants fed irregularly and oftener than every three hours. The reason apparently is that the stomach has not been given time to empty itself completely before more food is offered, and satisfactory results usually follow the lengthening of the feeding interval to four hours.

(D) **Unsuitable Composition of Food.**—In addition to food that has been contaminated by bacterial toxins or by the products formed from the milk itself by bacterial growth, other factors, both physical and chemical, may make milk so unsuitable to the newly born infant that vomiting is provoked: one is the large tough curd that forms in the stomach when raw cow's milk is fed. When undiluted cow's milk is fed, many babies seem to have a delayed gastric emptying time, due to the high alkaline buffer content of such milk. When milk mixtures particularly high in fat are used, delayed emptying of the stomach also tends to occur, and provokes vomiting. Milk itself, or one of the addition products, may also act as a specific allergen in the sensitized infant, provoking vomiting.

## II. OBSTRUCTION IN THE GASTRO-INTESTINAL TRACT

(A) **Esophageal Obstruction.**—In the newly born infant in whom the first attempt to offer water is followed by prompt vomiting or associated with apparent difficulty in swallowing, one should suspect at once esophageal obstruction. In such infants food or water are usually vomited unchanged, and a diagnosis can promptly and accurately be made by the use of opaque feedings and fluoroscopy or x-ray. Even though this condition is recognized immediately and a gastrostomy is made, and the infant fed by this route, he is unlikely to live any length of time because of the fact that, in addition to the atresia of the esophagus, there is usually a tracheo-esophageal fistula below the obstruction. Gastric juice with or without food may at any time be regurgitated

up into the esophagus and spilled into the trachea through the fistulous opening, and lead to fatal pulmonary changes.

In addition to congenital atresia, partial esophageal obstruction may also occur by compression from an enlarged thymus or heart.

(B) **Pyloric Obstruction.**—Contrary to the frequently made statement that vomiting in cases of congenital hypertrophic pyloric stenosis does not begin until about the third week of life, we note that not infrequently this symptom is

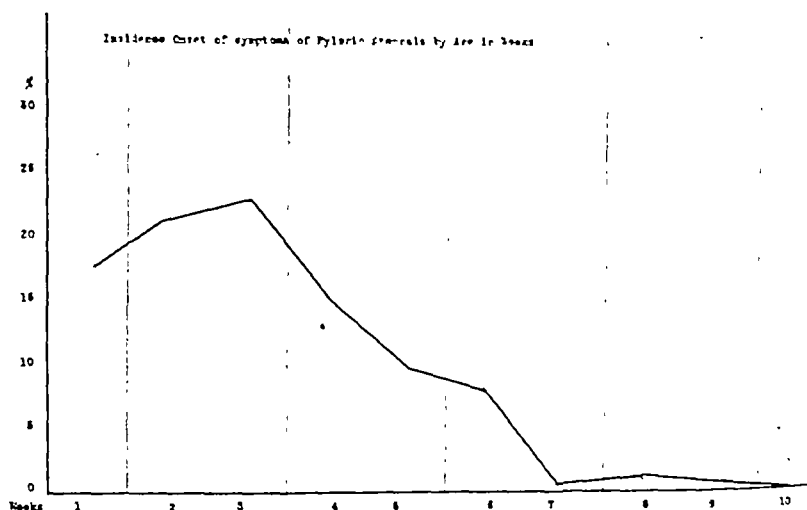


Fig. 38.—Incidence of onset of symptoms of pyloric stenosis by age in weeks.

fairly common even in the first week. From Fig. 38 it can be seen that in about 17 per cent of the cases observed at the St. Louis Children's Hospital during the period of 1916 to 1932 vomiting began during the first week of life, about 21 per cent in the second, and 23 per cent in the third. Cases subsequently admitted show the following incidence of onset: 16 per cent in the first week, 43 per cent in the second, and 20 per cent in the third. It is true, however, that the earliest vomiting in cases of pyloric stenosis is not usually as severe as it tends to become later. In this condition the vomitus is

characteristically unbile\* stained, strongly acid, and vomiting may occur at any time in relation to the feeding, and as it increases in frequency tends also to increase in amount and become projectile. This condition is usually quite readily diagnosed when one notes in addition to the above symptoms, the presence of exaggerated gastric peristaltic waves, whether or not the hypertrophied pyloric musculature (tumor) can be palpated; likewise a barium milk feeding usually gives characteristic fluoroscopic or x-ray findings, in that there is usually little or no initial clearance into the duodenum of the material, and a very greatly delayed emptying of the stomach, so that from four to six hours after a feeding almost the entire amount may still be present in the stomach.

Successful treatment of pyloric stenosis depends not only on the type of treatment used, but also on the early recognition of this trouble, and on the proper preoperative preparation and postoperative care. As may be noted from Fig. 39, the percentage of patients treated surgically increased steadily from 1916 to 1929, so that since the latter date practically all the patients admitted to the St. Louis Children's Hospital have been operated upon. The mortality varied inversely with the percentage of patients treated surgically. The operative procedure has been that of Fredet-Rammstedt, and has been described in detail by Clopton and Hartmann.<sup>1</sup>

*Preoperative Preparations.*—Satisfactory preparation for operation must include: (1) relief of dehydration and alkalosis, (2) at least partial restoration of glycogen reserves, (3) restoration of diminished plasma protein content and red blood

\* Since regurgitation of the duodenal secretions into the stomach is a physiological phenomenon, and since during the earlier stages of pyloric stenosis unquestionably considerable patency of the pylorus exists, it is indeed strange that such a remarkable lack of bile in the vomitus in this condition seems to occur. Recently we have noted associated "coffee grounds" vomitus and tarry stools in an infant who at operation was found to have pyloric stenosis, and in whom a Fredet-Rammstedt operation was followed by complete correction of the condition. There was a question, however, of the presence of a gastric ulcer adjacent to the upper edge of the pyloric musculature which had an unusually sharp edge.

cell volume, and (4) control of infection. Ringer's or lactate-Ringer's solution should be administered subcutaneously or intraperitoneally to relieve dehydration and alkalosis, dextrose to abolish ketosis and restore glycogen reserves (a 10 per cent solution given intravenously), and citrated whole blood (intravenously) to restore plasma protein and red blood cells.

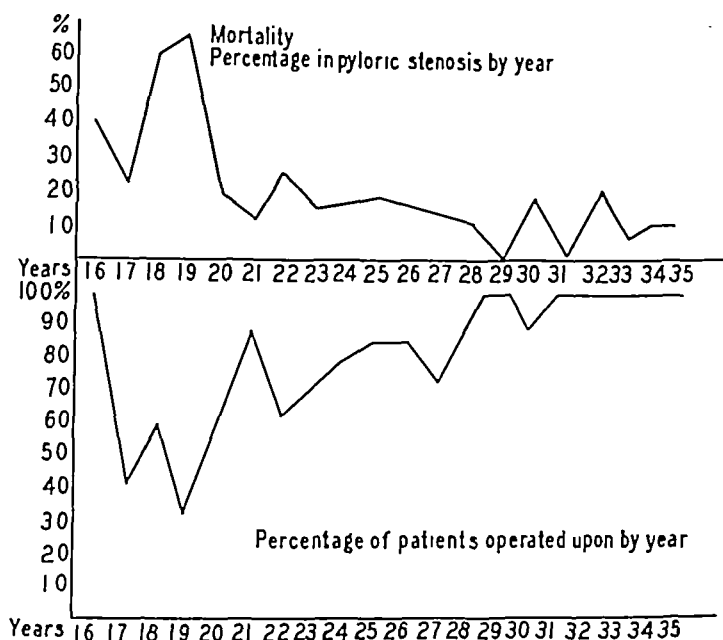


Fig. 39.—Percentage of patients with pyloric stenosis operated upon by year, and percentage of mortality in pyloric stenosis by year.

As often as not, otitis media will be present, and requires myringotomy and nasal treatment to control the infection.

*Postoperative Care.*—Experience has gradually taught us how best to take care of such infants after a successful operation. One of the most important points concerns the manner of feeding. The routine at the St. Louis Children's Hospital at present is as follows: two hours after operation  $\frac{1}{2}$  ounce

of sterile water or 10 per cent buffer water\* is offered, and two hours later  $\frac{1}{2}$  ounce of a formula. (If the baby has been breast fed and breast milk is available, it should be used instead.) The formula consists of equal parts of evaporated milk, 20 per cent buffer water and sterile water to which is added enough carbohydrate in the form of Karo syrup to provide a final addition of 4 to 5 per cent. For the first twenty-four hours the formula and water administration are continued alternately every four hours, the volume of each being kept at  $\frac{1}{2}$  ounce. During the next twenty-four hours the quantity of each is raised to 1 ounce, during the third day to  $1\frac{1}{2}$  ounces, etc. After about one week the buffer solution can be discontinued and the usual 1 per cent lactic acid diluent substituted. Also, the formula may be made more concentrated by omitting all or part of the sterile water. It has been our experience that this type of feeding accomplishes two purposes: (1) the increase is slow enough to make postoperative vomiting extremely rare, and (2) the addition of the buffered lactic acid apparently is very effective in preventing the Zed reaction of Zahorsky.<sup>2</sup> It is our belief that this postoperative phenomenon is due to the presence and growth of *Bacillus coli* high in the small intestinal tract, which are permitted to multiply rapidly as soon as the pylorus is made patent by the operation, and in that respect it is very much like the more common type of nonspecific diarrhea seen in young babies during hot weather, or associated with parenteral infection.<sup>3</sup>

(C) **Duodenal Obstruction.**—Occasionally an infant is born with atresia of the duodenum. This is usually below the common duct, and gives rise quite early to vomiting. Vomiting is likely to be projectile, but bile-tinged. Just as in pyloric stenosis visible gastric peristaltic waves may be seen.

\* Concentrated buffer solution has the following composition:

U.S.P. lactic acid (75-85 per cent) . . . . .	150 cc.
10 per cent sodium hydroxide . . . . .	200 cc.
Water to make . . . . .	1000 cc.

By 10 per cent buffer water is meant a 1:10 dilution of this concentrated solution.

Stools continue to be meconial, and may be entirely uncolored. When duodenal obstruction exists as the only congenital malformation of the gastro-intestinal tract, and is not accompanied by atresia elsewhere, its prompt recognition becomes important, since operative correction by gastrojejunostomy usually leads to excellent results. Not infrequently the lesion is not that of complete atresia, but just narrowing, and occasionally congenital bands may produce duodenal obstruction. Much the same symptoms may result, and treatment also requires surgical correction. The preoperative preparation and the postoperative management are identical with that for pyloric stenosis outlined above.

(D) **Anal Obstruction.**—Imperforate anus may be present at birth and eventually lead to abdominal distention and vomiting. Vomiting comes on rather late, however, in this condition, which should never be undiagnosed since a careful examination makes its presence readily discernible. The correction, of course, is surgical. Occasionally the anal obstruction is just a narrowing of the lumen of the bowel at or just above the internal sphincter. In such instances digital or instrumental dilatation, frequently repeated, may prove effective in relieving the obstruction.

### III. INFECTION

(A) **Enteric.**—Enteric infections are very rare in the newly born breast-fed baby for obvious reasons. In bottle-fed babies, however, despite the usual precautions taken, the intestinal tract is soon invaded by the colon bacillus group. Not infrequently on the third or fourth day after birth there is distinct fever with some vomiting and frequent bowel movements, which coincides with the infestation of the bowel by *Bacillus coli*. Other organisms, however, such as the members of the typhoid dysentery family, are more prone to lead to digestive upsets, characterized by vomiting and diarrhea. Such infections, however, are very rare in the newborn.

(B) **Parenteral.**—Almost any parenteral infection of a degree sufficient to produce fever may be accompanied by vomiting in the newborn or young infant. This is particularly true of upper respiratory tract infections, and especially when there is otitis media. The exact cause for this is not thoroughly understood, and probably depends upon at least three factors: (1) nasal obstruction accompanying the rhinitis, which interferes with nursing and probably leads to considerable swallowing of air, (2) swallowing of organisms draining down from the nose, and (3) absorption of bacterial toxins.

Second only to respiratory tract infections in producing vomiting is infection of the urinary tract. It is not uncommon to note evidence of pylorospasm during acute pyelitis, and vomiting may be quite projectile. In addition to pylorospasm, frequently abdominal distention develops, which may further increase the tendency toward vomiting. Omphalitis with involvement of the peritoneum likewise is not an infrequent cause for vomiting in the newborn.

#### IV. DERANGEMENT OF CENTRAL NERVOUS SYSTEM

(A) **Intracranial Conditions.**—Birth trauma with hemorrhage giving rise to increased intracranial pressure usually is associated with vomiting. So likewise is meningitis. In such cases vomiting occurs at any time in relation to food intake, and apparently is not accompanied by nausea, and is not likely to be associated with diarrhea.

(B) **"Autonomic Imbalance."**—Not infrequently one meets young infants who tend to be hypertonic and show evidence of gastro-enterospasm. This subject has received considerable attention in pediatric literature, and is reviewed in this number by P. J. White. The condition is looked upon as due to autonomic imbalance, and as part of the pylorospasm, vomiting may be a common occurrence. This condition can usually be distinguished fairly easily from real hypertrophic pyloric stenosis in that frequent stools rather than constipation are the rule, and the vomiting is usually re-



lieved fairly completely by the use of sedatives and drugs capable of relaxing smooth muscle spasm, such as phenobarbital and atropine.

(C) **Habit.**—Occasionally in young infants, but not in newly born ones, one may see habit vomiting fairly well developed. Shortly after a feeding the infant may be noticed to move its jaws, ruminate, and finally vomit. It gives the appearance of vomiting deliberately. Treatment may be at times difficult for this type of vomiting, and thick feedings which make vomiting more difficult are often of assistance, together with mechanical devices that may prevent jaw motion. The maintenance of the erect or semi-erect position after feeding, and the free use of sedatives are also indicated.

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### THE DIFFERENTIAL DIAGNOSIS OF DISEASES OF THE BREAST

THE differential diagnosis of diseases of the breast concerns itself with the separation of the inflammatory from the neoplastic processes and the further division of the latter into benign and malignant classifications. In a group by itself is the condition usually referred to as chronic cystic mastitis and its recognition in its various forms and its relation to carcinoma adds considerably to the difficulty in diagnosis of breast conditions. The various diseases, themselves, remain the same as in the past; but our conceptions of the etiologic factors are changing, due largely to a better understanding of the intimate relationships between a certain group of hormones and the breast. This is especially true of chronic cystic mastitis and the tumors, but does not obtain in inflammations of the organ.

In dealing with a patient presenting herself with the complaint of some disorder of her breast, a careful history is the first essential point. This should go back as far as the patient can recall any unusual changes in her breast. The feeling is that breast symptoms are intimately bound up with the menstrual history, so that the onset of menses, their regularity and duration, should be noted and whether or not there has been any pain in, or enlargement of, the breasts either immediately preceding menses, or during the intermenstrual interval, or at a time corresponding to ovulation. The number

of pregnancies should be noted, whether or not these terminated in normal deliveries, and if so whether or not the child, or children, was nursed and for how long. If a pregnancy terminated in a miscarriage or abortion it is important to know at what month and whether there were any complications, such as pelvic inflammatory disease which quite often follows an induced abortion. The presence of other pelvic disease should be ascertained, such as tumors or cysts, which the patient may know she has or for which she may have previously been operated upon.

The next step is the examination of the patient and in addition to the usual complete physical examination, special attention, of course, is paid to the breasts and the pelvis. For the breasts the patient is first examined in a room with good light, preferably from a window, and is seated facing the source of light. The points noted are the size of the breasts, of the nipples, and their relative position, also whether or not a tumor mass can be seen. This is further determined by palpation which enables us to decide whether there is a definite tumor present and if so, its consistency, its mobility, and whether it is separate and distinct from the rest of the breast parenchyma or intimately fused with it. The consistency of the rest of the suspected breast tissue and of the opposite breast is also noted. Axillary lymph nodes are best palpated with the patient in a sitting position. The arm is abducted and the examiner's hand is inserted as high as possible into the axilla. The palm of his hand faces medially and presses against the chest wall. This means that the right hand of the examiner explores the left axilla of the patient and vice versa. With the hand high in the axilla, the patient's arm is now brought back as close as possible to the chest wall and the palpating hand is brought down out of the axilla. Any existing axillary nodes are now felt between the hand and the chest wall. The patient next lies down and the examination of breast and axilla is repeated, making additional note of flattening out of the skin over the tumor and the presence of supraclavicular nodes.

Whenever possible, a pelvic examination should be made as it is an important part in the examination of every patient with a breast tumor, particularly if the presence or nature of the latter is questionable. If a definite tumor is present the presence of pelvic disease will not alter any proposed operative procedure, but the added information may change the postoperative course of treatment or such information may be of value in the future care of the patient. The above remarks concern themselves mostly with tumors; the possible relationship of these to pelvic disease and hormone influence will be discussed later.

#### INFLAMMATORY DISEASES OF THE BREAST

The etiologic factors in the true inflammations of the breast are not as obscure as with the neoplasms. As usual, we classify inflammations as acute and chronic, the former being more frequently encountered.

**Acute Pyogenic Mastitis.**—This is the type usually referred to as breast abscess or pyogenic mastitis because of its intensity and the organism or organisms causing it. It most often is associated with lactation and is probably a quite common occurrence. Its exact frequency cannot be determined because many of these patients are treated at home or at their doctor's offices and only a relatively small percentage of the cases find their way to the clinics or hospital wards. Because of its association with lactation, acute pyogenic mastitis is a disease of younger women, of those in the childbearing period of life. Instances before puberty and after the menopause are very uncommon and when they do occur are more apt to be infections or abscesses of the adjacent tissues which secondarily involve the breast. These, of course, are not associated with lactation and one also occasionally encounters true breast abscesses in younger women who are not lactating. Such infections we assume to be hematogenous in origin; and where there is a history of trauma preceding the infection, then the further assumption is that the hematoma

or traumatized tissue acted as an area of decreased tissue resistance (*locus resistencia minoris*); and the bacteria, lodging there from the blood stream, found local conditions more favorable for their growth. In the usual case of pyogenic mastitis associated with lactation, the bacteria enter the breast by growth along the lymphatics which follow the excretory ducts. These lymphatics are much more prominent and patent during lactation than in the resting breast, and the bacteria enter them through cracks or fissures in the skin of the areola and nipple. What begins as a lymphangitis rapidly extends into the very cellular hyperplastic parenchyma. The invading organism usually is the *Staphylococcus*, either alone or with some other micro-organism. Infections due to other bacteria alone, such as *Streptococcus*, *Pneumococcus*, *Bacillus typhosus*, have been described but are uncommon.

There is no proof that the bacteria cannot enter the breast by traveling up the lactiferous ducts, but if this does happen it must be in ducts filled with stagnant secretion; otherwise the flow of the secretion would carry the organisms down before they could gain access to the substance of the breast. Our feeling is that the bacteria enter the periductal lymphatics through cracks, fissures or abrasions on the nipple or areola, giving rise to an acute lymphangitis. The organisms then very quickly find their way into the breast parenchyma, which is now very cellular as it is composed predominantly during lactation of glandular epithelium. This tissue is not resistant to infection and very easily undergoes disintegration and liquefaction, giving rise to one or more abscesses. Several of the latter may fuse into one large abscess. From such a mode of origin one understands how one breast alone may be involved and how the infection may be limited to only a portion of that breast. Bilateral acute pyogenic mastitis does occur, but not very frequently, and the infection may be simultaneous or one abscess may follow its predecessor by an interval of several months during the same period of lactation. Recurrent infections in different periods of lactation may also occur and an individual is just as liable to the in-

fection during one lactation as during another. The general feeling, however, is that more abscesses occur following the first pregnancy, and this is supposed to be due to the fact that the thin skin covering the nipple and areola is not as resistant in the beginning of the first period of lactation as later. The gross and microscopic picture of a breast abscess is that of an acute pyogenic infection anywhere else on or immediately beneath the body surface and the pathology of such an abscess need not be discussed here.

The differential diagnosis of the usual acute pyogenic mastitis should present no difficulties. The patient is a young woman who has not gone far into her period of lactation. The affected breast is wholly or partly reddened, tender, larger than the opposite one, shows increased local heat; in short, all the cardinal signs of an acute localized infection. There is enlargement and tenderness of the regional axillary lymph nodes and these may break down and form secondary abscesses. Because of the induration, the breast is firmer than the unaffected one and the nipple is at a relatively higher level. The patient has some degree of fever and there should be a leukocytosis with an increased proportion of polymorphonuclears. The difficulty in diagnosis is found in those abscesses not associated with lactation, or in those cases not accompanied by the usual general and local manifestations of an acute infection. A patient recently seen illustrating the latter was a thirty-nine-year-old multipara, delivered of a normal child a month previously. Following this delivery she noticed that her left breast was hard and larger than the right. There had been no increase in size during this month and there was no pain, local heat or tenderness. The breast parenchyma did not transilluminate as the adjacent fatty portion of the breast did. The temperature was normal. The impression up to this point was that of carcinoma in a lactating breast. Aspiration biopsy was then done and pus only was recovered. Accordingly, incision and drainage of the breast was carried out. No explanation can be offered why the abscess occurring in this lactating breast should not have

given the train of acute symptoms and findings usually seen in such cases. When occurring in a nonlactating breast an abscess may simulate a solid tumor in that the pus may be under such tension and so covered with subcutaneous and breast fat that fluctuation cannot be elicited. We have seen such abscesses where also the mass made its appearance some weeks or more previous to the first examination and had grown slowly during the interval and without the local or general accompaniments of an abscess. In our experience these few cases have been mistaken for large solid tumors such as fibro-adenomas. Although the temperature may be normal, there will be a leukocytosis and an aspiration biopsy will reveal the true nature of the lesion and indicate the subsequent treatment.

**Chronic pyogenic mastitis** may occur but where found it is considered a sequela of a previous abscess. The acute mastitis involving a lactating breast usually disappears following incision and drainage. This rapid healing may be aided by the involution occurring in such a breast, inasmuch as the mother is not allowed to, or cannot nurse at the involved breast. Sometimes this rapid healing does not take place, especially where the abscess is involved in a nonlactating breast, and the sinus or sinuses following drainage may persist. This is due to the failure of collapse of the abscess cavity and to the fact that it contains active infected granulation tissue, which keeps up the discharge.

**Tuberculous Mastitis.**—The other chronic inflammatory process involving the breast with any degree of frequency is tuberculosis. Since this disease was first described in the breast by Sir Astley Cooper in 1829, about 500 cases have been reported, not a great number when compared with the incidence of pyogenic mastitis, carcinoma of the breast, or tuberculosis elsewhere in the body. Roughly, about 1 per cent of breast tumors are said to be due to tuberculous mastitis. A few of these cases have been reported in males, but by far the most of them have been in younger women, most frequently married women who have borne children. In other words,

the marked changes in the breast incident to hyperplasia and regression may be predisposing factors. The infection is, of course, due to the tubercle bacillus which has been demonstrated in and isolated from the lesions. In a few instances the strain of bacteria was identified and the bovine found each time (Barker). This series is, however, too small to be taken as final.

The mode of entrance of the organism into the breast is also a subject of some dispute. The majority of writers feel that the infection is hematogenous, although there is no proof of this and no explanation can be given for the lodging of the bacteria in the breast. There are others who feel that the infection is by retrograde lymphatic extension, pointing to the frequency with which tuberculous axillary lymphadenitis has preceded the lesion in the breast. The third possible mode of entrance is by duct extension into the breast from a tuberculous infection in an immediately adjacent tissue, such as a tuberculous empyema or osteomyelitis. Another possibility is direct infection of the breast through an abrasion or crack in the skin of the nipple or areola. The disease is commonly divided into the primary and secondary forms. In the primary, it is limited to the breast and no tuberculosis can be demonstrated elsewhere in the body, nor has there been a history of previous infection. The opposite is the case with the secondary form. In various reported series, the primary cases are found about twice as frequently as the secondary ones. Many, however, maintain that all are secondary to infection in another part of the body which cannot be demonstrated at the time; in which respect the disease resembles tuberculosis of the kidney.

Tuberculous mastitis is usually unilateral. Deaver has described several forms of the process and these depend on the rapidity of progress of the disease, the amount of necrosis, abscess formation and fibrosis. In the nodular form one or more discrete tubercles arise in the connective tissue accompanied by marked lymphocytic infiltration which soon destroys the acini. The tubercles break down, undergo liquefaction



and the resultant abscess fuses with other adjacent ones and with the space formerly occupied by the acini, and one large or several smaller abscesses arise. There is some degree of fibrosis around all of this so that a hard mass is felt on palpation. Such an abscess may increase in size and eventually burrow through the skin to evacuate itself and leave a permanent sinus. In most instances the axillary glands are involved and enlarged. These also may break down to give rise to sinuses and cases are recorded where the axillary infection was noted before that in the breast. The other gross form of the disease is the sclerosing type. This is merely a slower, more indolent form in which fibrous tissue proliferation predominates and little or no caseation and necrosis occurs. These forms are not very distinct and often cannot be separated.

The diagnosis of tuberculous mastitis, as usually seen, often presents difficulties because of its resemblance to other conditions. If there is active tuberculosis elsewhere in the body, or a previous history of it in a woman with a slowly progressing, usually painless lump in the breast, tuberculosis should be considered. If enlarged axillary nodes were noted first and then the lump in the breast, again tuberculosis should be thought of. Where a definite abscess can be made out, or the latter has broken through the skin leaving a persisting sinus, the diagnosis may be easy. The abscess may be aspirated and the material obtained examined for bacteria, cultured and a guinea-pig inoculation done. The sinuses may be carefully curetted and the bits of tissue obtained submitted for microscopic section. However, we do not always have the abscess or the sinus or the preceding axillary adenitis or active tuberculosis elsewhere and so we may have only a patient with a lump in the breast, which may have been noticed several months, with no definite history or symptoms to aid in establishing a diagnosis. Such a mass is usually painless, not associated with secretion from the nipple and because of the sclerosis around the process the deeper layers of the skin may seem to be attached to it. The diagnosis then is made by exclusion and the differentiation from carcinoma is not an

easy one. Age of the patient is not an important point unless the individual is quite young, as many instances of both diseases are found in the thirties and over. The history and findings may be the same in both instances. A patient with previous or present tuberculosis may also develop cancer of the breast and we have seen cases of the latter disease where the axillary metastasis was noted before the primary tumor. The two conditions have also been described in the same breast. Transillumination of the breast may give no definite information. The next step should be an aspiration biopsy and if this should prove inconclusive then exploration of the breast with wide excision of the tumor area or even of the whole breast parenchyma for immediate examination should be carried out. In the final analysis, then, the diagnosis can be made only by direct gross and microscopic examination of the tissue. In the course of such a diagnostic procedure other neoplasms of the breast will be ruled out.

Pyogenic mastitis, acute or chronic, is differentiated by the history, local findings, leukocyte count, if acute, and finally by aspiration biopsy. The other chronic inflammatory diseases of the breast, such as lues, actinomycosis, etc., are so uncommon that they need not be discussed at this time.

#### TUMORS OF THE BREAST

The classification of tumors of the breast is now a very simple one. The cysts or cystic tumors are now considered variations of chronic cystic mastitis. The solid tumors are divided into the benign and the malignant and of these the former will be considered first.

**Fibro-adenoma.**—These are the simple fibro-adenomas and the intracanalicular fibro-adenomas. They are tumors found nearly always in women and make their appearance only after puberty. They may be found after the menopause, but this is very uncommon, the feeling being that in such cases the tumor began its growth before the menopause and was perhaps unnoticed until afterward. The simple fibro-aden-

omas tend to appear within a few years after puberty while the majority of the intracanalicular type are found later on, usually after the age of twenty-five. There may be no sharp distinction between the tumors, and a simple fibro-adenoma quite often has areas of intracanalicular change in it. The writer feels that the simple fibro-adenoma, if left alone, will later become an intracanalicular one. The frequency of these is difficult to determine. In the Laboratory of Surgical Pathology of Washington University, their incidence was about equal to that of carcinoma of the breast and both the simple fibro-adenoma and the intracanalicular one occurred with about equal frequency. This may or may not be the experience in other clinics, but the general opinion is that these solid benign tumors are being seen more frequently than they were twenty-five or more years ago. The reason for this is largely due to the dissemination to the lay public of information concerning cancer. With the general realization that early cancer of the breast can be cured, more women are seeking medical advice much sooner after first noticing a lump in their breasts. This means that breast lesions are being seen earlier in their course and more of the benign tumors are encountered.

The cause of the growth is known in part. According to Cheate, the simple fibro-adenoma is the result of the localized proliferation of the pericanalicular connective tissue. In his studies he has identified the fine layer of elastic tissue that surrounds the ducts and even some alveoli. Immediately outside this layer is the peculiar cellular connective tissue intimately associated with the ducts. This connective tissue is not the same as the interlobar connective tissue which acts as the general supporting framework of the whole gland. In response to some stimulus, so far not definitely known, this pericanalicular or periductal connective tissue undergoes proliferation which remains localized and, hence, the whole mass is encapsulated. Similarly there is another layer of this same connective tissue immediately within the elastic tissue layer and when this begins to proliferate the connective tissue follows the path of least resistance and protrudes into the duct

lamina, giving rise to the typical intracanalicular fibro-adenoma. The nature of the stimulus causing this proliferation is not definitely known. Since the tumors appear only after puberty, the assumption is that one or more of the newly secreted ovarian hormones may be responsible. Some corroboration of this has been produced by Lewis and Geschickter, who demonstrated large amounts of theelin in a fibro-adenoma. Turner and others have demonstrated proliferation of duct epithelium and extension of the duct system following injection of theelin in experimental animals; but localized tumors have not been produced. Whatever the stimulus may be, it is probably the same with both types of these solid tumors with the extra-elastic connective tissue being more sensitive to it at first or during the earlier years of menstrual life.

Both types of tumors may be single or multiple or bilateral. They may vary in size, from a small nodule barely palpable to a tumor 10 cm. or more in diameter. They are characterized by the fact that they are completely encapsulated, freely movable, not attached to the overlying skin and may be separated from the rest of the breast parenchyma. Very often they involve that projection of breast tissue pointing toward the axilla. As the tumor increases in size it replaces normal breast parenchyma so that with a large tumor very little gland may be left to function. Upon gross section of a simple fibro-adenoma the cut surface is white to pink in color, firm, and the small, round punctate areas representing the duct openings may be seen with the naked eye or with a hand lens. The cut surface of an intracanalicular tumor is also white but on spreading the tissue between the thumb and fingers of each hand a series of clefts and cracks is seen. These are the distorted and elongated ducts formed by the protrusion of the proliferating connective tissue into their lumina. Microscopically the simple fibro-adenoma presents a background of connective tissue in which are embedded varying numbers of small round or ovoid ducts. The relative amounts of fibrous tissue and ducts vary, depending upon the degree of proliferation of the latter. Epithelial

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and connective tissue cells are all uniform in appearance and no microscopic evidence of malignant growth is made out. In the intracanalicular fibro-adenomas the connective tissue stroma contains many irregular clefts, cracks and slitlike spaces which are lined with cuboidal epithelium. These are ducts seen in an ordinary fibro-adenoma, but here collapsed and distorted by the growth into them of the proliferating intra-elastic connective tissue, pushing the lining epithelium as it grows.

If undisturbed certain changes may take place in both these tumors, the first being lactation hyperplasia. The duct system in either type of fibro-adenoma will undergo the same degree of proliferation as the rest of the breast. Ducts elongate and alveoli sprout at the ends of them. The secretion, however, accumulates in this abnormal duct system because it is not connected with any of the normal lactiferous ducts and the lactation hyperplasia persists in the tumor area long after the normal part of the breast has undergone postlactation involution. The pain associated with this trapped secretion is marked, because it causes marked dilatation of the ducts and the resultant pressure from this distention induces pain. Quite often a patient has been unaware that she harbored a fibro-adenoma until its great increase in size and persistence due to lactation hyperplasia made it noticeable.

Another change is that occurring mostly in the intracanalicular type of growth. This is a myxomatous change in the connective tissue which may be so marked as to give the cut surface of such a tumor an irregular mucoid appearance. Accordingly, the term *intracanalicular myxoma* or *fibromyxoma* has sometimes been applied to them. This same change may occur in the simple fibro-adenomas, but must be very uncommon, the writer having seen it only once. This myxomatous change is assumed to be due to some interference with the blood supply of the tumor. The third possible change in a fibro-adenoma is malignant proliferation of the connective tissue, resulting in a sarcoma. When encountered this has always occurred in the intracanalicular fibro-adenoma and

Bloodgood stated that he had never seen this malignant transformation in a woman younger than twenty-five. In our experience it has always occurred in much older women and never in the simple fibro-adenomas. As far as can be determined, malignant proliferation of the duct epithelium (carcinoma) in either of these solid tumors has not been found.

The differential diagnosis, then, of the fibro-adenomas concerns itself with separating them from the carcinomas and the determination of whether or not they are malignant. An early or small localized area of carcinoma may have some of the characteristics of the fibro-adenomas, such as lack of pain, mobility, absence of palpable or lack of enlarged lymph nodes and nonretraction of the nipple. However, most of the carcinomas will have enough infiltration into the surrounding tissue to give some degree of flattening of the overlying skin. Neither will transilluminate and where the age incidence is not an important factor an aspiration biopsy can be done or, preferably, an exploratory operation with excision of the suspicious mass and a surrounding zone of normal parenchyma. When we consider the size of the fibro-adenomas as usually seen, a carcinoma of similar size should ordinarily give some of the unmistakable signs of malignancy. To determine whether or not an intracanalicular fibro-adenoma is already malignant, the best method is excision and direct examination. Presumptive evidence is a solid tumor known to have been present for a long time (as much as several years) in a patient well along in adult life, who has noticed a recent, sudden, rapid increase in the size of the tumor.

**Chronic Cystic Mastitis.**—In a group by itself is the condition usually referred to as chronic cystic mastitis. The discussion concerning its nature has been active ever since Cooper first described it in 1837. We are perhaps beginning to understand some of the factors in its etiology but our main interest in it still lies in the fact that it may be a forerunner of carcinoma. The frequency of chronic cystic mastitis cannot be determined. No doubt a small percentage of the cases come to the doctor's attention. As will be pointed out later,



some of the changes included under this disease may be found in more breasts than hitherto suspected, in women approaching or passing through their menopause. Unless there is marked pain associated with the disease or unless the envelope of fat surrounding the breast parenchyma is absent or very thin, thus allowing her to detect the lump by palpation, a woman may harbor the condition without being aware of it. It is found almost always in women, but one does occasionally encounter a dilatation of the ducts in the breast of a male which may give rise to a tumor and the gross and microscopic picture of chronic cystic mastitis. It is always a disease of adults and the majority of the cases are found from about the age of thirty-five on. This is especially true of the cystic forms of the disease. Infrequently, diffuse solid masses are found in the breasts of younger women but these are often found to be due to connective tissue or alveolar epithelial proliferation with nothing more than moderate dilatation of the ducts. Previous lactation seems to have no bearing on its appearance. Its exact cause is not known but present-day evidence points more and more to its being the result of some disorder in ovarian secretion.

As a result of Taylor's careful studies we recognize the fact that there is no constant microscopic picture of a resting breast. The relative amounts of connective tissue, alveolar and duct epithelium vary greatly in normal or symptomless breasts. We do feel that there is some response in the breast to the changes in ovarian hormone activity incident to menstruation. Some feel that the changes grouped under chronic cystic mastitis are the end-results of the cumulative effect of this ovarian activity. This has been corroborated experimentally where dilatation of the ducts and desquamation of their lining epithelium has been produced following injection of smaller animals, notably mice, with theelin. Such a picture simulates chronic cystic mastitis. At any rate the disease most often makes its appearance at a time when the sex hormone balance of the woman is undergoing a marked rearrangement. Instead of there being a simple regression of the breast com-

ponents, as probably occurs in most cases, there is a proliferation of the connective and epithelial tissues, with the resultant varying picture included under this term. The disease is usually a slowly progressing one and it may or may not be attended with pain. The lesions are felt as lumps or isolated areas of increased hardness in the breast. They may be multiple or bilateral, but usually are single and involve only one breast. No satisfactory explanation of this has been made and it is one of the objections to the idea that the process is in response to ovarian hormone imbalance. If that were the case one would expect the process to be diffuse and bilateral. Extreme cases have been described where a large cyst or series of cysts have ruptured through the skin resulting in persisting sinuses. These are rare today. Instead we see a breast with a diffuse area of hardness due to small multiple cysts, connective tissue and small duct proliferation. This is the type in which we see more epithelial proliferation and often localized groups of small ducts are seen resulting in the picture referred to as nonencapsulated adenoma or fibro-adenoma. Into some of these dilated ducts or small cysts there is desquamation of lining epithelium and into others a papillary proliferation of lining epithelium. In other cases there is the large single cyst, often referred to as a blue-dome cyst, surrounded by a number of smaller ones in the neighboring firm parenchyma. These large cysts usually have a smooth, glistening lining which is made up of a single layer of epithelial cells. Papillary epithelial proliferation into such large cysts is not so frequent. Occasionally small cysts are found lined with large cells with markedly eosinophilic cytoplasm, with or without papillary proliferation. These have been interpreted by some as modified sweat gland cysts or adenomas. In other instances, the firm mass is found to be due to diffuse proliferation of the pericanalicular connective tissue, embedded in which are slightly to moderately dilated ducts, the latter often containing desquamated epithelium. Usually no epithelial proliferation is seen here and this type of change is more frequently found in younger women. Cheatle has given this the term of *mazo-*

*plasia* and finds that it may persist for many years with no tendency to malignant transformation.

The diagnosis of chronic cystic mastitis is made on the history of a slowly progressing, diffuse area of hardness in the breast, which may or may not be associated with pain. One is struck by the fact that most of the patients with this lesion have thin breasts where the fatty envelope is atrophic, thus allowing the individual to detect an area of hardness that a woman with fat breasts could not feel. Where the mass is felt in the latter type of breast, it is usually very large and more often associated with pain. The age of these women is important in that they are approaching or passing through their menopause or are still menstruating beyond the age when the menopause should be expected. In addition to this, the local findings are those of a diffuse or poorly localized tumor in the breast. This is not as freely movable as a fibro-adenoma and cannot be as easily separated from the breast parenchyma. In marked cases the mass may seem adherent to the deeper layers of the skin, thus simulating carcinoma. If there are one or more large cysts the intracystic tension is so great that the sense of fluctuation cannot be elicited. Transillumination may reveal a large cyst but not always the smaller ones, especially if there is marked fibrosis of the surrounding parenchyma. Aspiration should result in the recovery of cyst contents, if the cyst is punctured. One should not lose sight of the fact, however, that carcinoma may develop in chronic cystic mastitis and that the recovery of cyst contents does not exclude carcinoma in the neighboring gland tissue.

The differential diagnosis of chronic cystic mastitis concerns itself with the exclusion of the fibro-adenomas, carcinomas and possible sarcomas.

The simple fibro-adenoma occurs at a much younger age than the usual chronic cystic mastitis. Pain may be present in both, but in the former the mass is encapsulated, freely movable, and not attached to the skin, a finding usually not present in chronic cystic mastitis. With the fibro-adenoma transillumination gives a solid shadow, while with the other,

light may be transmitted. The next possible step is aspiration with the recovery of cyst contents if a cyst is entered, otherwise the results may be inconclusive. Usually one does not have to go so far in diagnostic procedures because the age, encapsulation and mobility identify the fibro-adenoma. With an intracanalicular fibro-adenoma the only other difference is the possible higher age incidence.

*Carcinoma.*—Much of the discussion about chronic cystic mastitis has been due to its confusion with carcinoma. In many respects it is impossible to differentiate between chronic cystic mastitis and an early or moderately advanced carcinoma without operation and microscopic examination of the tissue. Both occur during the same age periods, both are nonencapsulated, diffuse, cannot be separated from the rest of the breast parenchyma and are attached to the depths of the skin in many instances. In early carcinoma, absence of enlarged axillary glands means nothing. Transillumination may be inconclusive, depending on the size of the cysts, and aspiration may not always be positive as a small area of cancer may be missed. Here again the final appeal is carried to exploratory incision and examination of the completely excised suspicious area. These same diagnostic procedures are necessary to determine the presence of sarcoma.

*The Relation of Chronic Cystic Mastitis to Carcinoma.*—Ever since its description by Sir Astley Cooper one hundred years ago, discussion has concerned itself with whether chronic cystic mastitis is inflammatory or neoplastic. The consensus today favors the latter but opinion varies as to its relation to carcinoma. Ewing points out that in his experience about 50 per cent of the breast specimens excised for chronic cystic mastitis show proliferative changes that he interprets as definitely precancerous. He also makes the observation that very few breasts removed for and containing cancer "fail to show phases of chronic (cystic) mastitis in the outlying portions of the parenchyma." This has also been the writer's experience and he feels that in dealing with a possible chronic cystic mastitis one should always remember that such a lesion is

potentially malignant, at least where it is marked enough to give rise to a tumor or definite clinical symptoms. With more attention being paid to the prevention of cancer, the definite relation of this disease to chronic cystic mastitis should determine our course of treatment of the latter when it is encountered.

**Carcinoma of the Breast.**—Of the diseases of the breast, this is, of course, the most important. Its frequency cannot be exactly determined. We may get some idea of this from the mortality statistics; the last compiled for the United States being for the year 1933. In that year 128,489 deaths occurred due to malignant disease. Of these the deaths due to carcinoma of the breast were 12,484, this number being exceeded by carcinoma of the stomach, 26,566 and of the uterus, 15,221. All these show increases over the preceding years. Roughly, one might say that there are about 20,000 new cases of cancer of the breast in this country each year. The relative frequency to other diseases of the breast has varied greatly in recent years. A generation ago nearly 90 per cent of the breast tumors seen were malignant. Today less than 50 per cent of the tumors of the breast seen in consultation are malignant and if one includes chronic cystic mastitis as a breast tumor, the percentage of cancer is even lower. This is partly the result of the campaign begun twenty years ago by Bloodgood and Cullen to enlighten the lay public about cancer, and the realization by the public that early cancer of the breast can be cured. Women are seeking medical advice sooner after first discovering the lump in their breasts, hence more benign lesions are seen and cancers are seen earlier in their course. The disease is found mostly in women, only 1 per cent of cancers of the breast being found in males. Cancer of the breast is a disease of adult life and occurs most frequently in that decade when the menopause usually takes place, between forty and fifty. This may vary somewhat from clinic to clinic. In Harrington's carefully studied series of 4038 cases, 51 per cent were in women under fifty years of age. If one were to plot a curve of age incidence, the peak of such a curve would probably be be-

tween forty-five and fifty years. The youngest case recorded was in a girl of seventeen and it has been seen in women over eighty. Below thirty its incidence is very uncommon, but after thirty-five there is a rapid rise in frequency which remains high until fifty-five. Previous lactation, as far as can be told, does not influence the disease, as it is found in women who have never lactated. Lactation hyperplasia occurring at the same time the cancer is discovered influences the prognosis adversely since in such a breast with its abundant blood supply and increased lymph drainage the disease runs a very rapid course and instances of cure by any means are exceedingly rare, if they occur at all. The relation of ovarian function to the growth of cancer is not yet well understood, but there is certain evidence pointing to such a relationship. The observation was first made fifty years or more ago that the disease ran a relatively less malignant course in women who had ceased menstruating. This formed the basis for the oophorectomies done years ago in these women in addition to removal of the tumors. Somewhat later the artificial menopause was produced by x-radiation and in recent years Dresser has renewed this work. Further evidence is the experimental production of cancer of the breast in male mice following the injection of folliculin (theelin) first done by Lacassagne and since repeated by many others. According to Novak about 6 per cent of women pass through their menopause after the age of fifty. In a series of cases of cancer of the breast occurring in women beyond the age of fifty, the writer found that over 50 per cent of these women, instead of the expected 6 per cent, had such a delayed menopause. The only conclusion to be arrived at from all this is that ovarian function, through the elaborated hormones, is a factor, so far not completely understood, in the production of cancer of the breast. Trauma in the sense of a single injury has never been definitely proved to cause cancer. The chronic irritation of repeated minor insults may do so, but where a single injury is suspected of doing it, the presumption is that the lesion was already present and was aggravated or attracted attention by the blow.

Heredity has been recognized in recent years as one of the factors influencing the development of cancer. Many instances have been observed of so-called "cancer families" and the work of Slye has placed this on an experimental basis.

Cancer of the breast may arise from the epithelium in any part of the organ, the larger lactiferous ducts, the smaller ducts immediately draining the alveoli, or the alveoli. In the majority of cases the malignant proliferation starts in the smaller ducts. These are the ones usually dilated to form cysts in chronic cystic mastitis. There is a varying degree of connective tissue proliferation accompanying the cancer. The relative amount of this determines whether the tumor has the gross and microscopic characteristics of a scirrhus or medullary cancer. In the former there is abundant fibrous tissue proliferation and in the latter less. Often the two cannot be differentiated in the gross, and microscopically both may be seen in the same primary tumor. Less importance is placed on this differentiation today than in the past. The main thing is that the tumor is malignant. When the process arises in the alveolar epithelium it takes the form of an adenocarcinoma. Cancer arising from the lining of the larger ducts, according to some opinions, also gives the picture of adenocarcinoma. The writer feels that this is not so and that instead the malignant tissue confines itself to these larger ducts, giving the picture of a so-called duct cancer. The medullary and scirrhus cancers together make up most of the breast cancers, only 15 per cent being adenocarcinomas, and the other unusual types are found very infrequently. Grossly the tumor is nearly always single and begins as a painless lump. Pain is a relatively late symptom. Usually one breast is involved although simultaneous bilateral cancer does occur. This is quite uncommon, but when it does happen, the prognosis is very poor. Cancer may occur in a surviving breast, after the other has been removed or treated for the same disease. Naturally, the shorter the period between the appearance of the first and second tumor, the less favorable is the prognosis. Where the period is of any appreciable length one may assume that the

second tumor is a cancer independent of the first. It does not necessarily follow that the second is a late recurrence of the first. The gross and microscopic picture of the second tumor may differ from that of the first. The usual description of a carcinoma of the breast, retraction of the nipple, axillary metastasis, dimpling of the overlying skin, etc., applies to fully developed and advanced cases and is so well known that it need not be repeated here. We are concerned with the early cases, where the above characteristics have not yet made their appearance and about all we have to deal with is a small lump in the breast. This is usually painless, freely movable, most often not attached to the skin and not accompanied by axillary metastasis. The presence or absence of the latter is of great importance in the prognosis. In the series recently reported by Harrington, 71 per cent of the patients with cancer of the breast without axillary metastasis were living five years after operation, 55 per cent lived ten years after operation and 40 per cent were alive fifteen years after. With axillary metastasis present at the time of operation only 26 per cent lived five years or more, 13 per cent were living after ten years and 9 per cent lived fifteen years postoperatively. With all the scattered information we have today concerning this disease, the presence or absence of axillary metastasis is the most important factor we have in estimating the prognosis, yet today about 72 per cent of the patients with cancer of the breast, when first seen, already have axillary metastasis. This merely means that our patients are seeking medical advice still quite late in the course of the disease. Harrington found that the average length of time elapsed between the discovery of the lump in the breast and the seeking of medical advice, even in recent years, was fourteen months. In some individual cases that period had been several years. This certainly means that our patients are not yet being seen as early as they should be.

The diagnosis of carcinoma of the breast is based on the patient's history and physical findings. The usual history is that of a painless lump in the breast, often accidentally discovered and growing slowly. In the early cases the findings



may not be characteristic, that is, nothing but the tumor mass or area of hardness is felt and the findings of advanced carcinoma, such as attachment to the skin, dimpling of the skin, lack of mobility, and retraction of the nipples, are missing. Transillumination may show a dense area that does not transmit light. Aspiration biopsy may show the malignant cells, but negative findings do not rule out carcinoma. The differential diagnosis is the ruling out of any benign lesion and these are solid tumors, such as the fibro-adenomas, and chronic cystic mastitis. This should not be difficult when we are dealing with a well-developed cancer, but with the small or early lesions a differential diagnosis cannot be made until the tumor or tissue from it is examined grossly or microscopically. Transillumination may show a large cyst, but it cannot give definite information about a small solid tumor. Another minor diagnostic procedure is the aspiration biopsy. This is the removal of a very small bit of the suspected tissue through ordinary or specially adapted hollow needles by means of suction. In the hands of some this has given very satisfactory results. In order to obtain tissue for a corroborative diagnosis of a clinically definite cancer of the breast which is to be radiated, we feel that it is of value, but we also feel that its value is questionable when resorted to as the final means of diagnosis in early or doubtful cases. With a small tumor, if we obtain malignant tissue, all well and good, but in a small tumor the actual area of cancer may be missed. We also feel that this method should not be used unless, if malignancy is proved, active treatment, whether surgical or radiological, is to be instituted immediately. Traumatization of a malignant lesion may increase the rate of growth and should be avoided. We have preferred, in the small or early tumors, or those where direct examination of the tissue is necessary, to excise the suspicious area with a good zone of normal neighboring gland. One should be very careful not to incise the tumor itself. This excision of the tumor can very often be done under local anesthesia through a small skin incision, but it should always be done in the operating room with the patient prepared for a

mastectomy, if the tumor is found to be malignant. The nodule is removed it is handed to the attending surgeon or pathologist for examination or, what is better, if the surgeon is as well grounded in tumor pathology as he should be, he bisects the tumor and makes the diagnosis from the gross appearance. If the tumor is malignant, he must, of course, wash his hands, remove his gown and gloves before proceeding further. The person examining the tissue must be trained in tumor pathology, whether he be pathologist or surgeon. If the tumor to him is definitely malignant on gross examination, then it is a routine case and the patient's interests are best served by closing the wound and waiting twenty-four to forty-eight hours for well prepared paraffin sections, which can then be examined by the pathologist at his leisure and without the feeling that he must hurry because a patient is waiting on the operating table until his diagnosis is made. We have never felt that a frozen section can tell one more than can be seen with the unaided naked eye. If the diagnosis cannot be made with the gross specimen, then well fixed and prepared sections are in order. We have occasionally seen the diagnosis of chronic cystic mastitis made on a single frozen section and nothing more done to the patient. Then when the rest of the excised tissue has been carefully examined by means of sections taken from several areas, a small zone of cancer has been found and unless this possibility has been provided for, the patient has to be told of the earlier mistaken diagnosis and urged to submit to the radical mastectomy.

Because of lack of space the above discussion has had to be brief and many lesions not commonly met with in the breast have not been referred to. An earlier article by the writer goes into these in more detail. Our main problem in diseases of the breast is to recognize cancer and to do it as early as possible. A lump in the breast should never be temporized with. Even today, too many women are seeking medical advice with lumps in their breasts which they have been aware of for some time and in many instances their medical advisers have not insisted on immediate diagnosis and treatment, but because of the pa-

tient's age or lack of faith in operative cure for cancer, or other reasons, have preferred to watch the lump from time to time. We feel that every lump in the breast in an adult woman should be considered malignant until definitely proved otherwise. No doubt there are many practitioners who can do this by the ordinary means at their disposal, but with the increasing frequency with which we are seeing these early questionable lesions, we feel that the coordinated efforts of the patient's personal physician, the pathologist, the radiotherapist and a surgeon who has special training in neoplasms are necessary. To fill these needs the so-called "tumor boards" or "tumor clinics" have been organized in many hospitals and medical centers. There such cases are seen, studied and discussed and a plan of treatment agreed upon, depending upon the findings in each particular case. With the diagnosis and treatment of early cancer our goal, and with diagnosis and treatment organized in such a manner today, we feel that in many of the instances the responsibility is too great for the physician to assume alone.

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ECZEMA AND ENVIRONMENT

ONE of the most frequent diseases of the skin met with in general as well as in dermatological practice is "eczema" or "dermatitis." These terms are used almost synonymously. However, the term "dermatitis" includes "eczema" in that the former word is used in connection with certain other diseases not related to eczema at all. When the true cause of the inflammation is known, the word dermatitis is usually used with a preceding modifying word, *e. g.*, "contact dermatitis." If, however, the cause is undetermined, a general diagnosis of "eczema" is offered as a name for the condition (Norman Walker).

Under the heading of "eczema" may be included a group of simple inflammations of the skin. Since there are a number of unrelated factors involved in the production of a rather wide variety of clinical pictures, "eczema" does appear to be a group rather than a single disease.

**The Clinical Picture.**—This depends upon both the type of lesion present and the distribution. The appearance varies from an acute, red, weeping surface to a chronic, thickened scaly skin with accentuation of the natural lines commonly called "lichenification." The primary lesions are usually vesicles and occasionally simple erythema. The intense pruritus associated with these lesions results in traumatizations of various kinds, which alter the picture; for instance, the scratching in the vesicular types of the eruption produces secondary in-

fection (papules and pustules), and crusting follows. The erythematous types may become vesicular and a similar picture supervenes. In the more chronic or subacute types thickening of the skin and scaling may appear.

The distribution may vary from an entirely local inflammation, acute, subacute or chronic, to a partly or fully generalized eruption. It may be symmetrical or asymmetrical, depending upon the factors influencing its production. A bilateral and symmetrical distribution may often imply a circulatory dissemination of the causative agent. The asymmetrical eruptions are usually of external origin.

**The Histopathological Picture.**—In a few words this may be summarized as follows:

The epidermis and the corium are both involved in a primary edema. In the epithelium this edema is extracellular and intracellular with "balloon" degeneration, thus producing intra-epidermal vesicles. In very acute, weeping eczema the keratinized layer may be lost entirely. If it be present, there is often parakeratosis. Due to hypernutrition, the rete may be thickened and the pegs elongated (acanthosis). In more chronic cases there may be hyperkeratosis. The upper cutis shows engorgement of the vessels, general edema and often a cellular infiltration. The histopathological picture, of course, depends largely upon the acuteness or the chronicity of the disease.

**Etiology.**—Eczema occurs in individuals of all ages and both sexes and from a wide variety of causes. The mechanism involved may be divided roughly into three types. First, ordinary irritation, such as may occur in the majority of people from the application of strong chemicals. Second, that type of specific hypersensitivity named "atopy" by Coca. Third, contact dermatitis.

It is pertinent here to mention certain fundamental differences between these latter two types of hypersensitivity, because the mechanism involved is quite different. Coca contrasts these two diseases very strikingly. Atopy appears to be an antigen antibody reaction. At least in the blood of the

atopic individual the presence of "reagins" may be demonstrated by passive transfer of specific sensitivity to a small area of skin in a normal nonsensitive individual. Heredity is of prime importance in the development of atopy. Furthermore, only 7 per cent of whites are subject to atopy in any form, including hay fever, asthma, migraine, etc. Urticaria is the most usual type of atopic skin reaction. Eczema is very rarely, but may be, of atopic origin.

Contact dermatitis accounts for the greater number of eczema cases. In this disease the mechanism is unknown but reagins are not demonstrated to be present by the passive transfer test. Heredity is a factor of minor importance in the production of this sort of hypersensitivity, since it has been shown by Bloch and others that at least 70 per cent of the white race may be sensitized at will to certain contact agents.

The work of Brown, Milford and Coca on contact dermatitis due to ragweed pollen throws light on another phase of this problem. These investigators found that in cases of eczema due to ragweed pollen the patch test was positive with protein-free oil extracts of the pollen, but scratch and intradermal tests with pollen protein were negative. The exact reverse was found in cases of hay fever due to ragweed pollen. Thus, they showed that eczema was due to the pollen oil and that atopic hay fever was due to the pollen protein.

*Rôle of Trauma.*—Trauma plays a major rôle in the production of eczema. It is an extremely pruritic disease and mechanical trauma, such as rubbing and scratching, is always indulged in by the patient. This increases the inflammation, denudes the surface, and may be the most important factor in starting secondary infection. Strong irritating local applications, such as sulphur, tar, resorcin, mercury, and other chemicals, may be sufficient in themselves to cause inflammation. These are applied to an already inflamed surface so that the resulting acute inflammation may mask whatever underlying condition is present.

The state of the skin capillaries must also be considered here. Peterson has studied capillary permeability by means



of the cantharides blister test and by qualitative and quantitative analysis of the protein content of the tissue juices found in the blister fluid. He reports that differences of capillary permeability are present in individuals of different types and also in various general constitutional conditions and diseases. Our clinical studies indicate that capillary permeability is particularly increased over the entire surface of the skin when any part of it is involved in an inflammation, such as eczema. As a result, at such a time the skin will be much more reactive and more easily inflamed by any trauma.

The importance of trauma may be illustrated by the following case:

A child two years old with a generalized eczema was found to be sensitive to the ingestion of wheat. The eating of a cracker would produce an intense itching over the body. The baby was put in the Barnard Free Skin and Cancer Hospital for treatment and study. Wheat was removed from the diet and local applications applied. When the skin was completely free from eruption, the following experiment was performed. The left arm and leg were dressed in a stiff, thick, crinoline bandage and 2 wheat crackers fed the child. Within two hours there seemed to be an intense pruritus all over the body. The child rubbed and scratched vigorously and by next morning patches of eczema were present all over the body. However, when the dressing was removed from the left arm and the left leg, there was no evidence of any eruption whatsoever in the covered areas. It was concluded that ingestion of wheat, to which the patient was sensitive, produced an allergic pruritus and that the severe trauma of rubbing and scratching on the already disturbed skin (increased capillary permeability) caused the visible signs of eczema. The fact that no eruption occurred under the covered areas demonstrated that the visible lesions on the uncovered portion were due to trauma. Probably most allergic infantile eczemas are produced in much this same way. We have performed similar experiments several times and have obtained similar convincing results.

**Eczematids.**—There are many diseases in which a general-

ized secondary eruption occurs as a result of the dissemination of micro-organisms from a primary focus. These are often referred to by the suffix "id." As examples there are syphilids, tuberculids, epidermophytids, etc. Toxic substances may produce an "id" in a similar manner. Denny has reported generalized secondary eruptions in cases of local picric acid dermatitis. We refer to this phenomenon in cases of eczema as "eczematid." Eczematids are far from infrequent. They are due probably to the absorption of toxic products at the site of the primary acute eczema. Whether such an inflammation produces something toxic to normal cells, what these toxins are, and whether they are absorbed into the general circulation are questions of theoretical nature and not as yet proved. Reasoning, however, by analogy it seems a likely explanation of the basis of the eczematids. As was mentioned before, there is a generalized increase of capillary permeability. These toxic substances escaping from the capillary bed into the papillae of the skin cause local insult and death of cells in the upper cutis and epithelium with a resulting acute inflammation. For example, in varicose dermatitis of the legs a secondary eczematid is frequent on the backs of the hands and arms, symmetrically distributed. The eczematid may be quite generalized, as in the following case.

*Illustrative Case.*—A woman forty-five years of age applied a mustard plaster of her own making to her chest as treatment for upper respiratory infection. This resulted in the burning of an area of skin about 6 inches square. The area was covered with large bullae, was red and edematous, with a weeping exudate which dried forming a crust. In the course of the next few days there appeared a generalized symmetrical eruption consisting of groups of tiny papules and dry vesicles.

This latter eruption was evidently due to the absorption of toxic products from the initial lesion on the chest. Since capillary permeability over the entire skin was greatly increased, the dissemination of toxic products to all parts of the skin was accomplished via the blood stream. The cells sur-

rounding capillary beds in the papillae were bathed in lymph containing these toxins and the generalized inflammatory reaction (eczematid) resulted.

**Hereditary Diathesis.**—There are undoubtedly people born into the world with a distinct hereditary predisposition to eczema, just as there are hereditary predispositions to tuberculosis, cholecystitis, hypertension, and other diseases. This predisposition was originally called by Czerny "exudative diathesis." Such a patient may begin with eczema in his first month and continue with outbreaks during childhood, during puberty, or throughout life. The skin of such an individual seems to be highly reactive, so that inflammation may be easily produced by both specific and nonspecific causes. The skin capillaries are easily thrown into a state of increased permeability and the physicochemical equilibrium of the skin is quite easily upset. Such a patient may have a whole list of specific sensitivities, and contact dermatitis may be produced by a variety of agents. Atopy may sometimes be a factor in this condition. The ordinary wear and tear of life, such as heat and cold, sun and wind, dust, soap and water, secondary infection, and other irritating factors are of varying importance. Thus, the study of a case of chronic exudative diathesis is very difficult, and all the factors mentioned in connection with eczema have to be taken in consideration. Patch tests are particularly deceptive because false, nonspecific positive results are often obtained. The same may be said of intradermal and scratch tests with protein extracts of atopic antigens.

**Constitutional Factors.**—Opinion is divided as to the importance of constitutional factors in the production of eczema. Adamson believes that the disease is entirely external. Ingram, however, points out that many constitutional conditions influence the course of eczema and are sometimes the underlying cause. One of us (Engman, Sr.) has emphasized for many years the importance of the general constitutional condition in eczema patients. Such diseases as nephritis, hepatitis, hypertension, heart disease especially with early de-

compensation, tuberculosis, diabetes, thyroid dysfunction, and so on, cause sufficient disturbance of the general constitution to produce disequilibrium of physicochemical relations in the skin, particularly changes in capillary permeability. The skin, as much a part of the body as any other organ, is affected by functional disturbances. Eczema from any cause, or combination of causes, may result more easily in the skin of a patient suffering from certain constitutional disorders than in one whose general status is normal.

*Illustrative Case.*—The patient was a woman forty-three years old complaining of chronic eczema of the hands and feet. The skin of the palms and soles was chronically inflamed and markedly keratotic. The redness was sharply outlined at the borders of the palms and soles. Her general examination showed an increase in weight, slow pulse, vague muscular pains, sense of fatigue, nervousness, and a minus 20 per cent basal metabolic rate. Under proper thyroid medication all of these symptoms improved greatly and the eruption on the palms and soles cleared up in two or three months. This type of eczema we call "thyroid eczema" in that thyroid dysfunction is the underlying cause. The eczema is produced on the soles by much walking and on the palms by household work, such as washing clothes and dishes, polishing furniture, and scrubbing floors.

*Illustrative Case.*—The patient was a man sixty-five years old who had a dermatitis over the lower legs, ankles and on the backs of the hands, of several months' duration. General examination and electrocardiogram showed some myocardial changes and enlargement of the heart, but no very marked heart disease. The patient complained of severe itching of the legs. He had been using various strong patent preparations to allay the itching. The eczema cleared up rapidly under soothing local applications, rest, and small doses of digitalis.

The interpretation of this case is as follows: the myocardial changes reduced, somewhat, the efficiency of the heart. A very mild dependent edema resulted which was more or less

chronic. There was itching of the legs due to the microscopic edema in the skin with consequent trauma both mechanical (scratching and rubbing) and chemical (strong local applications). These factors produced an eczema on the legs, and an eczematid on the backs of the hands from the general increase of capillary permeability and absorption of inflammatory toxic products. Rest and digitalis improved the efficiency of the heart, which was the underlying condition, and since the traumatic factors were eliminated, the skin healed.

**Secondary Infection.**—Secondary infection is a contributory factor in a great number of eczema causes. An inflamed skin especially if excoriated may offer a fertile medium for certain organisms particularly the staphylococci. Pustulation may take place, or as the eczema clears up it may be followed by a series of furuncles.

Infection may be a primary cause of an eczematous eruption—eczematoid dermatitis as first described by Engman, Sr.

**Handling of Patient.**—The study of a patient with eczema follows no set rule. Each problem must be dealt with individually. There is, of course, always the possibility that the distribution of the eruption may give some clue as to the probable cause. For instance, eczema of the eyelids is usually produced in one of two ways: first, by local application of some cosmetic such as mascara or eyebrow pencil; second, by something with which the hands come in contact. It is a very human habit unconsciously to rub the eyes so that whatever the hands have on them will be rubbed on the eyelids.

*Illustrative Case.*—The patient was a woman thirty-two years of age, with an eruption around both eyes consisting mainly of an erysipelas-like, red edema extending in all directions from the eyelids for about an inch, and involving the lids themselves. Her physician had made a tentative diagnosis of erysipelas. However, the consultant decided the eruption was due to an external contact agent because the patient was feeling well, had no temperature, and the eruption was so exactly symmetrical. Mascara proved to be the causative agent.

*Illustrative Case.*—A neighborhood night watchman had

repeated attacks of eczema involving the left eyelid. It was quite difficult to discover what the causative agent might be. Wearing of gloves did not help the situation. Careful questioning as to the duties of this patient revealed that he carried his flash light in his right hand and would try the door of a store with the left hand, at the same time flashing the light through the window. A certain bank had a brass door pull, which was covered with brass polish occasionally. A patch test with this brass polish was positive. Evidently the left hand came in contact with the brass polish and later the patient would rub his left eye with his left hand.

**History.**—The history of the present eruption, of all past eruptions, especially of a similar nature, and of the general habits of the individual is, of course, the greatest source of data in solving any case. If the patient presents himself for advice as soon as the eczema appears, the trail is much more easily followed. The patient's memory is fresher regarding where he has been and what contacts he has made immediately preceding the appearance of the eruption. If many days since the onset have passed, it is much more difficult to obtain contact data, and it is sometimes necessary to wait for another attack, in order to trace the causative agent. Absolute co-operation on the part of the patient is most necessary. Strangely enough, this is frequently hard to get. Some patients refuse to devote any thought themselves to possible contacts. Such a person will answer questions indifferently, even hostilely, in which case it is next to impossible to make any headway.

**Patch Tests.**—The patch test offers great assistance in discovering the cause of eczema in many particular cases. The technic is simple. A suitable area of skin is chosen, such as the anterior forearm just below the cubital space, lateral surface of the upper arm, the anterior thigh, or the abdomen. In these areas the skin is perhaps delicate enough to make positive patch tests more likely. The material to be tested whether liquid or solid is placed on a small piece of gauze 1 cm. square. The gauze is applied to the intact skin and over

it is laid a piece of cellophane 4 cm. square. Adhesive is placed with a wide margin over the whole patch. Forty-eight hours later the patch is removed. There will be, in a positive test, a small square patch of eczema corresponding to the square of gauze. If adhesive irritates the skin, there will be a margin of clear skin around the center positive patch test. Thus, there will be no confusion as to what has produced the little patch of eczema. In case the patient is extremely sensitive to the material tested, there might be a very severe reaction if the patch is left on two days. Therefore, it is a good rule to remove the patch if the patient has very intense itching at the site of the test any time before the two days are up. Delayed reactions are sometimes encountered so that the test site should be watched for several days after the patch is removed.

The interpretation of positive patch tests is simple if one will consider two important points. First, there are many materials which will irritate the skin of most people. If such a common irritant is to be used for testing purposes, it is obvious that it must be in a sufficiently dilute solution so that the normal nonsensitive skin would not react. It is often necessary to control the test by applying the material in question in dilute solution to one or more normal subjects. Second, the interpretation of a positive patch test and its relation to the eczema under observation is analogous to the interpretation of a positive Wassermann in its relation to a lesion suspected to be syphilitic. True syphilitic lesions may be present and the blood may show a negative Wassermann test. On the other hand, a syphilitic with a positive Wassermann may have some other disease not connected with syphilis. Such laboratory tests are only an aid to diagnosis, and should not entirely govern the viewpoint of the clinical problem. It is quite possible that a patient may be sensitive to more than one thing so that though a certain material gives a positive patch test in a patient, that particular material may not have produced the eczema in question. These two factors in patch testing are very well illustrated in the following case:

*Illustrative Case.*—The patient was a young woman twenty-five years of age with an eruption on the cheeks, roughly corresponding to the rouge and powder areas. The most obvious probability was rouge and powder. Since these contain orris root a patch test was applied of orris root oil extracted after the method of Coca. The patch test was positive to a mild degree. The use of orris root free cosmetics did not improve the patient and it was discovered that the eruption was due to black gloves. A patch test with the black dye (paraphenylenediamine) was markedly positive. It was found on subsequent testing with orris root oil, that a mild positive reaction resulted in a certain per cent of normal non-sensitive individuals. Thus, our original interpretation of the positive orris root test was misleading and further study of the case was necessary.

**Common Contactants.**—It is important to note here some of the more common causes of contact dermatitis. These fall naturally into groups.

Cosmetics are of especial importance in reference to eczema of the face because of their universal use especially by women. The most frequent offending ingredients in cosmetics are orris root, perfumes, and pigments. Any cosmetic may be at fault, even the so-called "nonallergic" ones. Included in this group are the shaving preparations used by both sexes, hair dyes, hair tonics, finger nail polishes and enamels, and deodorants. Frequently a dermatitis may be caused by contact with a cosmetic on the skin of another person, as illustrated by the following cases:

*Illustrative Case.*—A man twenty-five years old developed a severe vesicular dermatitis on his lips and around his mouth. The cause of it proved to be a new brand of lipstick his fiancée was using.

*Illustrative Case.*—A middle-aged man presented himself with an eczema involving the face. For many months he reappeared at intervals with recurring attacks. Close inquiry revealed no contacts which had any etiological significance. During one acute attack, his wife appeared in the office with



him and it was quite apparent that she dyed her hair. Questioning revealed that the recurrences of the husband's eczema corresponded with the time of each fresh application of the wife's hair dye.

Dyes in general are frequent contactants. Dyes used in furs and clothing are common offenders.

*Illustrative Case.*—A housewife aged forty was seen in her home suffering from an acute vesicular dermatitis involving the face, neck, shoulders, extensor surfaces of the arms and forearms and the exposed area of the chest. Many remedies had been applied; several physicians had placed her on various diets. She was frantic with torturing pruritus. The disease had begun six months previous to our observation. History revealed that it came on shortly after the purchase of a new dress. A patch test with a fragment of the brown woolen material produced an extremely severe vesicular reaction. The patient discarded the dress and made a complete recovery in a few weeks.

Oliver reported the first case of dermatitis due to the rotogravure section of the Sunday newspaper. It is noteworthy that these cases have exacerbations on Mondays. Such cases are not infrequent.

Plants of many species are responsible for a large group of eczema cases. Both the plant pollen carried in the air, and the leaf itself may produce dermatitis. Of the pollens, ragweed pollen is the best known offender. Such cases are usually seasonal. Direct contact with plants such as poison ivy, sumach and primrose produces an almost universally recognized dermatitis. Rarely many other plants may also excite a similar dermatitis.

Household chemicals form a group very seldom detected. Among them are included insecticides, antiseptics, soaps, deodorant soaps, cleaning agents, furniture and floor polishes and house dust (probably since some of the above agents are contained in it).

Occupations of various sorts expose patients to many substances to which they may be or may become sensitive. For

instance, cement workers sometimes become sensitive to cement, painters to paint or some of its ingredients, candy makers to flavoring extracts, and so on.

To these groups might be added a miscellaneous one including imitation pearl beads, jewelry, wool, mohair, feathers, etc. Medicines, especially patent preparations, are universally used to treat various mild skin affections. Many times a true sensitization may be present and a contact dermatitis be produced rather than a nonspecific chemical irritation. Thus, a few mosquito bites may be converted into an acute eczema.

**Treatment.**—Obviously the first and most important step in treatment is to discover and if possible eliminate the cause of the dermatitis in the individual patient. Contributory causes as mentioned previously should also be sought for and eliminated. This procedure has been discussed. Local treatment is usually necessary and must be chosen to suit the requirements of the case. The best rule to follow in general is to use soothing applications. In very acute weeping cases cold wet applications are most relieving. In more erythematous cases and in subacute eczematous conditions lotions containing bland powder, creams, and bland pastes are useful. To allay the itching phenol in 1 per cent or at the most 2 per cent solution or mixture may be added to the lotions or ointments. Strong chemicals usually used for eczema, such as tar, sulphur, resorcin and salicylic acid, should be used with great caution, or better, not at all. Boric acid, oxide of zinc and corn starch are safer and give much better results. Secondary infection is relieved by adding 4 per cent xeroform to the applications.



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### THE TREATMENT OF GONORRHEAL VAGINITIS

GONORRHEAL vaginitis is understood to be an infection of the vagina caused by the gonococcus. This particular stage of a gonorrheal infection is rarely observed in the adult, as it seems to be only a transient phase in the development of this disease in the female. It certainly is more commonly seen in children and offers a very definite problem in therapeutics. As stated by Witherspoon<sup>1</sup>, "The treatment of gonorrheal vulvovaginitis in infants and young girls has always been an unsolved problem to the gynecologist, the pediatrician and the general practitioner. The various methods of therapy—vaginal instillations and irrigations, antiseptic applications to the cervix, the application of heat, the use of suppositories, change of bacterial flora and the administration of vaccines—have offered so little encouragement in the eradication of this condition that many physicians consider that no treatment at all is of equal value. Therefore, it was with great enthusiasm and with a warm reception that those who came in contact with this disease welcomed the rational hormonal therapy first advanced by Lewis<sup>2</sup> in 1933.

"Lewis' method of therapy is based on logical clinical reasoning. Gonorrheal vulvovaginitis is usually limited to the prepuberal years. For reasons clearly explained by Schauffler and Kuhn<sup>3</sup> on the basis of microscopic study, the immature

vaginal mucosa harbors the gonococcus in its crypts and offers a fertile means for its growth. With the onset of puberty and the conversion of the infantile vaginal mucosa into the mature, thickened stratified epithelium, the gonococcus no longer finds a fertile habitat, and the vulvovaginitis of childhood disappears. In fact, it is rare to observe gonorrheal vaginitis in a woman. The rationale of Lewis' treatment was the conversion of the infantile vaginal mucosa into the mature type by administering the ovarian follicular hormone."

In an excellent historical review of therapy in gonorrhea, Wehrbein<sup>1</sup> states, "We may also mention its complications and so be assured that it is a problem worthy of great efforts. But the efforts must be less primitive; the disease is not known well enough. Its course without treatment cannot even be approximately stated with statistical figures; even with treatment we do not know yet if the average case may be expected to last two months or six months. Our pathological knowledge of the disease is still deficient. Where are the gonococci, how long do they last in near or remote foci, how are they slain or if this is too much what are their living conditions *in vivo*? Until some of these questions are solved it will be an accident if we find the means of shortening a gonococcus infection materially and it will be a miracle if we find a specific treatment."

Schauffler,<sup>5, 6</sup> and Schauffler and Kuhn<sup>3</sup> have given us an excellent description of the anatomy of the immature vagina and have indicated the reasons for the limitation of the infection to the vagina without the usual involvement of the accessory glands thereof. The lack of development in these glands does not predispose to their infection. They speak of the immature vagina as the "harbor of infection." They state, "We know that, in the adult, the gonococcus is retained in the Skene's and Bartholin's and the cervical glands, and is frequently passed over from the cervical glands to the endosalpinx, while the vagina, except for a transient inflammatory reaction, is immune. We have shown that, on the other hand, in the infant and small child, the vagina is the point of election—the Skene's, Bartholin's and endocervical glands are rela-

tively noninfectable, and there is immunity of the endosalpinx secondary to that of the endocervix.

"It is not sufficiently clearly understood, even by those who have made something of a study of gonorrheal infections in infants, that the vaginal cervix is the seat of deep pleats and folds similar in all respects to those noted throughout the remainder of the vaginal wall, thus, the vaginal cervix is not exempt from an infection which involves the entire vaginal wall. This fact was early noted by Hess in a series of post-mortem examinations. Unfortunately, Hess' observation had been misconstrued. In his own report Hess carefully differentiates between the vaginal cervix and the endocervix. He reports infections of the vaginal cervix only. He has been broadly quoted to the effect that at postmortem he has demonstrated 'cervical infections,' with the inference that endocervical infection has been described. This inference is not justified. The use of the term 'cervicovaginitis' to describe such infection, while it is perhaps more minutely descriptive, we believe is misleading in that it suggests a frequent involvement of the endocervix as an accompaniment of vaginal infections. Endocervical infection as an integral part of the pathology occurs only in individuals who have reached a stage of advanced development of the cervical glands. It is perhaps an occasional transient accompaniment of severe acute infection of the immature vagina. The use of the descriptive term 'vulvovaginitis' is distinctly a misnomer. The vulvar irritation in these cases is completely secondary, and due to factors similar to those which cause external irritation in pyelitis, diarrhea, etc."

Ruys,<sup>7</sup> in the discussion of the etiology of vulvovaginitis infantum, states that "the first question is whether or not it is a gonorrheal infection. The clinical picture of this infection is not typical enough to allow a diagnosis to be made without a bacteriologic examination. The diagnosis is almost always made on smears of the pus stained by Gram's method or only the methylene blue. Cultures are not considered necessary. As there are some cocci that resemble the gonococci more or less when different staining methods are used, the way to a

faulty diagnosis is open. Clauberg<sup>8</sup> pointed out that many cases of vulvovaginitis were falsely considered gonorrheal infections. From 70 children with vulvovaginitis he could not cultivate gonococci. Gradwohl<sup>9</sup> cultivated gonococci in only 2 out of 25 cases." Ruys found "the ascites-Levinthal-agar plates and blood-water-agar plates excellent mediums for the isolation of gonococci and tried to find out which part this microbe plays in the vulvovaginitis of children. All smears were stained by van Loghem's method. Since the diagnosis in children with vulvovaginitis is made by van Loghem's Gram method combined with the culture method, the number of children treated for vulvovaginitis gonorrhoea in the Amsterdam hospitals has been reduced from approximately 450 a year to twelve a year." Her conclusions were that "in many cases of vulvovaginitis the etiologic diagnosis can be made only by means of the culture method. For the examination of smears, van Loghem's Gram method gives the best results. Vulvovaginitis gonorrhoea occurs only in the acute form. Every case of vulvovaginitis gonorrhoea is complicated by gonorrhea of the rectum. In other forms of acute vulvovaginitis, hemolytic streptococci, influenza bacilli and diphtheria bacilli play a rôle. In chronic vulvovaginitis, probably the primary cause is a constitutional disease."

In our own<sup>10</sup> study of vaginitis in the Washington University Dispensary, we have used the Gram stain for all specimens and have checked our findings by the culture method, using Gradwohl's<sup>9</sup> media. The results showed that approximately 40 per cent of the children registered in our vaginitis clinic suffered from a specific gonorrheal infection. We have grouped the cases into specific and nonspecific vaginitis and have thereby reduced the total number of patients being treated for gonorrheal vaginitis to a very small group. The period of attendance for the nonspecific group has been greatly reduced. A positive diagnosis is made on demonstration of typical biscuit-shaped intracellular gram-negative diplococci on direct smear and culture of the organisms on the special hormone-agar media.

## TREATMENT

Vaccines of many different types have been used with very little consistent relief being obtained in most cases.

Innumerable antiseptics have been used for many years, the favorites being members of the silver group. In 1920, Gellhorn<sup>11</sup> proposed the use of 1 or 2 per cent silver nitrate in an ointment base. The duration of the disease was not greatly shortened by this treatment and at times complete failures resulted. Potassium permanganate has been used extensively in varying concentrations and seems to be of value, provided that the solution is 1:2000 or stronger. A solution of 1:1000 in my experience has given excellent results without any harmful reaction in the tissues.

Schauffler<sup>5</sup> in 1927 described his method of treatment by the use of an antiseptic incorporated in anhydrous wool fat as a base, and this antiseptic preparation was forced into the vagina under sufficient pressure to cause distention of the vagina and flattening of the rugae. In 1933, he reported with Kuhn<sup>3</sup> on the use of this method in over 2000 treatments with satisfying improvement in a large series of stubborn cases, in the majority of which several other methods had failed. They considered the method harmless and effective.

In 1928, Edgar Allen<sup>12</sup> demonstrated the transformation that could be effected in the vagina of the immature monkey by the administration of ovarian hormone. After the injection of 1005 rat units of ovarian hormone over a period of twenty-one days, the vagina of the monkey exhibited an epithelium averaging 30 layers in thickness and differentiated into two zones. The vaginal epithelium of the control monkey, on the other hand, remained 4 to 8 layers in thickness. Smears showed a proportional increase of partly or completely cornified epithelial cells. Associated with the vaginal changes there was some development of the cervical glands and an invasion of their lumina by many polymorphonuclear leukocytes. The endometrium was "built up" at most to a midinterval phase. Involution of the structures affected by the hormone occurred in a few weeks subsequent to the last injection of the hormone.



Lewis<sup>2</sup> asked, "Could a similar result be obtained in a child? A gonococcal infection in the vagina subsides when the delicate thin layered epithelium lining the vagina is converted into the thicker structure of the adult. Primary infection in the adult vagina is either extremely shortlived or nonexistent."

With these ideas in mind Lewis<sup>2</sup> began the study of the effect of theelin on gonorrheal vaginitis in children and in 1933 reported his results in a series of 8 cases. Subsequent to this several reports have been made showing the good results obtained by the administration of hormone therapy in varying doses by different routes.<sup>13, 14, 15</sup>

Witherspoon<sup>1</sup> reported that 10 children with gonorrheal vulvovaginitis have been unsuccessfully treated by the administration of the ovarian follicular hormone, amniotin. The criteria of lack of success are the persistence of the vaginal discharge and the presence of gram-negative intracellular diplococci in the vaginal smears. Several disadvantages of this method of therapy are pointed out, such as the harmful effect on the immature ovary by the hormonal action on it, cervical infection in addition to vaginitis as a focus of continuing the disease, the unpleasant features of the daily hypodermic injections, the occasional unfortunate secondary sexual changes, such as enlargement of the breasts, vulval hyperemia and hypertrophy, and lastly the high cost of this method of therapy.

It is very likely that the observations of Witherspoon are the result of inadequate dosage or because of the manner in which the hormone was administered.

Allen and Diddle<sup>10</sup> have checked the ovarian follicular hormone effects on the ovaries in an experimental way, using immature monkeys. There was definite reddening and swelling of the sexual skin and an increase in the size of the uterus was noted. The ovaries were studied immediately after the period of injection and also after a thirty-day recovery period. They concluded, as far as they could tell histologically, that there seemed to be little damage to the ovaries, and that the reaction was temporary. They state, "The therapeutic use

of comparable doses of this hormone in children may be prescribed without fear of harmful results upon the ovaries."

TeLinde and Brawner<sup>17</sup> conclude: "Amniotin administered orally or hypodermically in ethylene glycol solution is of no value in the treatment of gonococcal vaginitis. We have been unable to demonstrate any effect of the hormone on the vaginal mucosa or breasts. Amniotin in oil has proved effective both in the production of maturation of the vaginal mucosa and in its therapeutic action in gonococcal vaginitis in 72 per cent of the cases. In most of the patients receiving prolonged treatment breast hypertrophy was noted. Amniotin in suppository form has been proved to be effective in the production of mature vaginal epithelium and in its therapeutic effect in gonococcal vaginitis in all cases in which we have used it. This group included some cases which had been resistant to the hormone when administered hypodermically in oil. The epithelial change produced by the hormone, whether administered hypodermically or in suppositories, is transient, and there is no clinical or experimental evidence to show that its administration is harmful in dosage necessary to cure this disease. So far as our experience has gone we have concluded that amniotin administered in suppository form is superior to any other known method of treating gonococcal vaginitis."

Lewis and Adler<sup>18</sup> found that the estrogenic substance in ethylene glycol given hypodermically was relatively effective when used in large doses: 2400 International units daily. Eight hundred International units daily proved disappointing. Estrogenic vaginal suppositories (originally 600 International units and later 1000) proved very effective. They also noted that the administration of estrogenic substance changes the reaction of the vaginal secretions from neutral or alkaline to acid, and believe this to be a major factor in elimination of the gonococcal infection. The acidity of the vaginal secretions is easily measured and provides a sure guide by which one can determine whether or not dosage is adequate. They encountered no ill effects and consider this type of therapy harmless and also most effective.

Marion and Magnan<sup>10</sup> made a preliminary report on the treatment of vaginitis with: (1) a pyridium solution douche, (2) insertion of pyridium suppositories, (3) oral administration of pyridium tablets. Details of their cases and the percentage of pyridium in the suppositories were not noted in their paper.

In 1934, we<sup>10</sup> reported a three-year study of the treatment of gonorrheal vaginitis by the insertion of vaginal suppositories containing 0.16 Gm. pyridium in a base of boroglyceride of gelatin, at bed time. This is followed by a cleansing douche of 1:1500 potassium permanganate (5 grains to 1 pint of water). It was possible to obtain negative smears and cultures in definite cases of gonorrheal vaginitis following the treatment by the suppositories alone. We have now studied about 50 cases of gonorrheal vaginitis treated satisfactorily by this method and feel that it is definitely effective, simple in application and has no harmful side actions. The average course of treatment extended over a period of from four to eight weeks, depending upon the cooperation of the patient in carrying out the treatment. Treatment should probably be continued for ten days to two weeks after negative smears are obtained. By means of this type of treatment any complicating urethral infection is taken care of by the fact that pyridium is absorbed from the vagina and is excreted through the urinary tract, bathing the urethra with a definitely antiseptic solution. The folds, as noted in the vaginal portion of the cervix by Schaffler,<sup>5</sup> are also treated by this method of application and it seems likely that reinfection of our cases has been less frequent than in other series because of these additional actions. The pH of the pyridium suppositories is approximately 4.0 and it is possible that this chemical reaction in the vagina enhances the action of the pyridium suppositories. The importance of the pH of the vagina will be stressed in the consideration of other methods of therapy.

Abrams<sup>20</sup> reports his impressions of the various types of therapy and finds, "A small percentage of the patients in the past who have had persistent positive smears have shown in-

volvement of the cervical glands. I feel that in a large series of cases it is possible this will occur even with the use of estrogenic substance and when smears do not become negative the cervix should be investigated by means of a small electrically lighted endoscope."

Crossen<sup>21</sup> reported on the treatment of gonorrheal vaginitis by diathermy and obtained consistently negative smears after twenty-nine weeks in the acute series. The average length of treatment required to give consistently negative smears in the chronic cases was a little over four weeks. The difficulties in applying this method of treatment to young children make it undesirable from a practical standpoint.

Notes,<sup>22</sup> discussing the routine treatment of gonorrhea in females, took a very definite stand against the antiseptic method of treatment, based upon his observations at the City Social Hygiene Clinic of the District of Columbia. He expressed the belief that the best method of treatment was to establish and maintain drainage of the various foci of infection encountered in the female tract. The creation of a local reaction and drainage was his final method of treatment in his clinic, and as a result a much larger number of patients were discharged from the clinic. Electrocautery was applied to the cervical glands at intervals of two months and 25 per cent silver nitrate solution was applied as a local irritant to the urethral meatus and cervix weekly. One drachm of 1 per cent lactic acid jelly was applied to the vaginal vault nightly in an attempt to establish a normal bacterial flora.

It is my practice in the treatment of adults with chronic gonorrhea on the Gynecological Service at the St. Louis City Hospital, to attempt the removal of foci of infection by: (1) coagulation of Skene's glands and (2) conization of the cervix. Joachimovits<sup>23</sup> in his book on gonorrhea of the female genital tract, highly recommends the Sturmdorf operation as a means of removal of local foci. Such a procedure is simplified by the use of the operation of conization with the Crossen electrode. A word of caution must be introduced to warn against the use of even superficial cautery in treatment in the acute stage, as

we have seen cases of severe pelvic peritonitis develop therefrom.

Karnaky<sup>21</sup> has studied the treatment of vaginitis in general in regard to: (1) the bacterial flora of the vagina, (2) the glycogen content of the vaginal mucous membrane, (3) the number of Döderlein bacilli present, (4) pathological conditions of the vagina, and (5) the hydrogen ion concentration of the vaginal secretions. He finds that there is a definite relationship between these five factors upon which depends the life and growth of vaginal micro-organisms. As a result of his study, he recommends a tablet containing an adequate amount of glucose in a form that can be utilized to supply the epithelial cells and nourish the Döderlein bacillus. Sufficient boric acid is added to establish a  $pH$  of 4.0 and produce a mild astringent action thus diminishing the amount of the discharge. Also incorporated in the formula is a quantity of "Diodoquin," a new quinoline ring giving it an iodine content of 63 per cent (5-7 Diiodo-8-Hydroxyquinoline). It is an insoluble and non-toxic compound and experiments which he has conducted prove its effectiveness in destroying organisms of the protozoan type. His treatment has also proved satisfactory in the treatment of gonorrheal vaginitis. The name of the preparation used is "Floradex." A very interesting diagram is shown, illustrating the life cycle of the vaginal epithelium, in which one sees the change in  $pH$  that occurs shortly after birth and remains until puberty, thereby allowing a definite change to occur in the vaginal flora of a child. He also illustrates the drop in  $pH$  during pregnancy when there is a marked increase in the presence of estrogenic substances in the blood stream of the mother and the epithelial layer of the vagina is greatly thickened. This latter factor may be of the utmost importance in the clearing up of a gonorrheal vaginitis as pregnancy proceeds to term.

In the Washington University Dispensary the treatment of gonorrheal vaginitis complicating pregnancy has been by means of potassium permanganate douches 1:1500 throughout the pregnancy, with the result that no gonococci could be demon-

strated in the genital tract of these cases at term. There have been no maternal or fetal complications in these cases.

The importance of the  $pH$  of the vaginal secretions in relation to the cure of gonorrheal vaginitis will now be considered. Lewis and Adler<sup>18</sup> stress this factor as the means of demonstrating adequate estrogenic therapy. They state, "It is of course of the utmost importance to determine the presence or absence of the vaginal response to estrogenic substance in all cases, as without this tissue change no benefit can be expected. This was formerly done by securing minute biopsies and examining sections with the aid of the microscope. This method is time consuming and expensive. Vaginal smears showing extraordinary desquamation of epithelial cells are evidence that the estrogenic reaction has occurred. The inexperienced observer will, however, often be misled, particularly if the exfoliation is not great. The gross appearance of the vaginal mucosa and introitus is frequently helpful. We wish now to stress the value of another simple practical test of the estral response which can be carried out easily in a few minutes. Long ago Döderlein<sup>25</sup> called attention to the presence of the bacillus named for him and considered its acid-forming properties as responsible for the acid reaction of the secretions of the adult female vagina. Zweifel<sup>26</sup> later showed that it was the destruction of the superficial glycogen containing cells of the vaginal mucosa that produces much of the acidity. In the thin vaginal mucosa of the child but little glycogen is contained. On the other hand, the superficial cells of the adult vagina and, of more importance to us, of the vagina of the child adequately treated with estrogenic substance are loaded with glycogen. These as a result of bacterial or enzymatic action produce a markedly acid reaction as they break down. Soeken,<sup>27</sup> Cruickshank<sup>28</sup> and others have described the histologic changes that occur during puberty and ordinarily before the occurrence of the first menstrual period. They have also pointed out the dramatic and abrupt change to acidity in reaction of the vaginal secretion which occurs at this time and that this in turn is accompanied by an equally rapid transformation of the vag-

inal flora. *In vitro* the gonococcus grows best in a faintly alkaline medium ( $pH$  7.2 to 7.6). If this is rendered acid very gradually over a period of days or weeks these organisms will rarely adapt themselves to a medium as acid as  $pH$  6 to 6.2. Usually the culture dies before this point is reached. Tests that we have carried out to determine the  $pH$  of the vaginal secretions of children in our series before treatment have given  $pH$  values between 6.8 and 7.4. With the appearance of the estrogenic reaction of the vaginal mucosa (checked by biopsy and microscopic section), the vaginal secretions became acid ( $pH$  4.5 to 6.2), nearly always giving readings below 6. Nearly every case in which the  $pH$  of the vaginal secretions dropped to below 6 recovered from the gonococcic infection. Consequently we believe this acid change of the vaginal secretion is the important curative factor produced by administration of estrogenic substance in gonococcic vaginitis of children."

Krumm<sup>29</sup> finds variations in the glycogen content of the vaginal mucosa as shown by the Schiller-Gram test to be a relative index to the quantitative amount of ovarian hormone present in the body. This test can, therefore, be used in checking the efficacy of estrogenic substances which have been given by various methods in the hope of obtaining a therapeutic response.

Adair and Hesseltine<sup>30</sup> have investigated the histopathology of vaginitis and the biochemical approach to therapy thereof. A mixture of lactose (95 per cent) and citric acid (5 per cent) was used with the result that definite changes occurred in the epithelial layers of the vaginal wall. The histological picture is restored to nearly normal including an increase in the number of glycogen granules in the epithelial cells. The use of lactose instead of glucose as the sugar in such treatment is emphasized in order that the development of mycosis may be avoided.

Oberst and Plass<sup>31</sup> studied the hydrogen ion concentration of human vaginal discharge by means of a quinhydrone micro-electrode and found it to be normally  $pH$  4 to 4.5 during the intermenstrual period. They also noted the corresponding

changes in the vaginal flora that occur with the changes in reaction.

We see, therefore, that a number of biochemical, endocrinological and histopathological factors must be taken into account if our therapy of gonorrheal vaginitis is to be rational.

#### CONCLUSIONS

1. Vaccines as yet have offered little aid.
2. In general the results of antiseptic treatment have been disappointing.
3. "Floradex" is apparently a rational therapeutic agent, but might be improved by the substitution of lactose for the dextrose used.
4. Hormone therapy is successful if the estrogenic substance is given by the proper route (as suppositories) in adequate dosage. There is apparently an appreciable number of recurrences. May these not be due: (a) to the development of cervical and endometrial glands, in response to the estrogenic substance (Allen<sup>12</sup>), which would predispose to the spread of the infection to areas which have not been involved in the original disease and upon the withdrawal of treatment these areas might act as foci and reinfect the vagina as it returns to its original immature state; (b) to the lack of treatment of certain original foci (*e. g.*, urethritis)?
5. We may still be unaware of certain by-effects of hormonal treatment which have not been demonstrated as yet, but may nevertheless be present and cause possible complications in certain patients at a later period in their development.
6. Pyridium therapy has been generally satisfactory in both specific and nonspecific vaginitis. It is (a) quite economical, (b) prompt in production of results, (c) easy of application, and (d) general in action as well as local, which may account for the lesser incidence of recurrences.
7. Progress in the treatment of gonorrheal vaginitis will be made if we continue to rationalize our therapy along biochemical and endocrinological lines. Perhaps the best results



can be obtained in certain cases by the use of various combinations of the methods discussed.

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# CUMULATIVE INDEX

- ABDOMINAL diseases causing fever in children, *July*, 21  
 Abortion, diagnostic mistakes, *July*, 76  
     habitual, *July*, 81, 93  
 Abscess, abdominal, in children, *July*, 26  
     mediastinal, in children, *July*, 18  
     of brain in children, *July*, 43  
     of breast, acute, *Sept.*, 627  
     chronic, *Sept.*, 630  
     of kidney, multiple, in children, *July*, 33  
     of lung, multiple, in children, *July*, 18  
     pulmonary bleeding in, *Sept.*, 486  
     perinephric, in children, *July*, 33  
     retropharyngeal, in children, *July*, 13  
     subphrenic, in children, *July*, 26  
 Acromegaly, *Sept.*, 387  
 Addison's disease, borderline cases, *Sept.*, 345  
 Adenoids, infected, fever due to, *July*, 10  
 Adiposis dolorosa, *Sept.*, 374  
 Adiposity, cerebral, *Sept.*, 374  
 Adiposogenital dystrophy, *Sept.*, 374  
 Adrenal cortical tumors, *Sept.*, 349  
     insufficiency, borderline cases, *Sept.*, 345  
 Allergic asthma, treatment, *Sept.*, 591  
     infants, colic in, *Sept.*, 512  
 Alternation of heart, *July*, 188; *Sept.*, 545  
 Amebic dysentery in children, *July*, 24  
 Anal obstruction in newborn, *Sept.*, 622  
 Anemia and hypothyroidism, *Sept.*, 340  
     sickle cell, *July*, 55  
 Appendicitis, acute, in aged, *July*, 133  
     in children, fever in, *July*, 25  
 Arcus senilis, *July*, 128  
 Arrhythmias, diagnosis and treatment, *July*, 175  
     significance of, *Sept.*, 537  
 Arsenic encephalitis, *Sept.*, 417  
 Arteriosclerosis in cardiovascular-renal disease, *July*, 209  
 Arthritis, gonorrheal, in male, *July*, 152  
 Asphyxia neonatorum, *July*, 99  
 Aspiration in pleurisy, *July*, 329  
 Associated movements, automatic, abnormal, *July*, 227  
 Asthenia, neurocirculatory, simulating hyperthyroidism, *Sept.*, 343  
 Asthma, bronchial, treatment, *Sept.*, 591  
     emphysema in, *Sept.*, 443  
 Atelectasis, pulmonary, in newborn, *July*, 106, 111  
 Ateliosis, *Sept.*, 362  
 Atopy, *Sept.*, 652  
 Auricular fibrillation, *July*, 181; *Sept.*, 541  
     flutter, *July*, 184; *Sept.*, 541  
 Auriculoventricular block, *Sept.*, 544  
 Australian X disease, *Sept.*, 424  
 Autohemotherapy in herpes zoster, *July*, 245  
 Autonomic imbalance in newborn, *Sept.*, 623  
 BASOPHILISM, pituitary, *Sept.*, 349, 387  
 Beet pulp, laxative value, *Sept.*, 457  
 Birth trauma, vomiting due to, *Sept.*, 623  
 Blepharospasm in parkinsonism, *July*, 228  
 Blood, disorders, genetic aspects, *July*, 253  
     pulmonary bleeding in, *Sept.*, 490  
     iodine, in hyperthyroidism, *July*, 286  
     vessels, diseases of, pulmonary bleeding in, *Sept.*, 489  
 Bones, diseases, in aged, *July*, 138  
 Botulism, *July*, 265  
     in children, *July*, 28  
 Brain abscess in children, *July*, 43  
     tumors in children, *July*, 47  
 Breast, diseases of, differential diagnosis, *Sept.*, 625  
 Brill's disease, *July*, 52  
 Bronchi, diseases of, causing bleeding, *Sept.*, 485  
 Bronchial asthma, treatment, *Sept.*, 591  
 Bronchiectasis as cause of fever in children, *July*, 18  
     pulmonary bleeding in, *Sept.*, 485

- Bronchitis, chronic, emphysema in, *Sept.*, 443  
     in aged, *July*, 135  
 Broncholithiasis, pulmonary bleeding in, *Sept.*, 486  
 Bronchopulmonary bleeding, diagnosis and treatment, *Sept.*, 483  
 Bronchoscopy in pulmonary hemorrhage, *Sept.*, 492  
*Brucella melitensis*, *July*, 51  
 Bulky foods, laxative value, *Sept.*, 449  
  
 CARUNCLE of kidney in children, *July*, 33  
 Carcinoma of breast, *Sept.*, 641, 642  
     of cervix, diagnostic mistakes in, *July*, 78  
     of lung, pulmonary bleeding in, *Sept.*, 487  
 Cardiac. See *Heart*.  
 Cardiovascular disease in aged, *July*, 139  
     physical exercise in, *July*, 191  
 Cardiovascular-renal disease, preventive aspects, *July*, 209  
 Cellulose in foods, *Sept.*, 450  
 Cereals, thick, feeding of, in gastroenterospasm, *Sept.*, 518, 519  
 Cerebral adiposity, *Sept.*, 374  
     edema and hemorrhage in newborn, *July*, 105, 109  
 Cervical lymphadenitis in children, *July*, 14  
 Cervix, carcinoma of, diagnostic mistakes, *July*, 78  
 Chickenpox, encephalitis in, *Sept.*, 433  
 Cholecystitis, acute, diagnosis, *Sept.*, 472  
     chronic, diagnosis, *Sept.*, 473  
 Cholecystography, intravenous, *Sept.*, 475  
     oral, *Sept.*, 478  
 Cholesterosis, *Sept.*, 473  
 Cogwheel motor rigidity, *July*, 232  
 Colds, common, as cause of fever in children, *July*, 9  
 Colic, infantile, classification and treatment, *Sept.*, 511  
 Colitis, ulcerative, in children, *July*, 24  
 Constipation and hypothyroidism, *Sept.*, 340  
     bulky foods in, *Sept.*, 449  
 Contact dermatitis, *Sept.*, 651, 653  
 Contractions of heart, premature, *July*, 177  
 Convulsions, uremic, treatment, *Sept.*, 532  
 Corpus spongiosum, marked induration, in gonorrhea, *July*, 155  
 Cosmetics and eczema, *Sept.*, 661  
 Cowperitis, gonorrheal, *July*, 155  
 Cramps and hypothyroidism, *Sept.*, 340  
 Cretinism, *Sept.*, 355  
 Cyanosis of newborn, diagnosis and treatment, *July*, 99  
 Cystic mastitis, chronic, *Sept.*, 637  
 Cystitis in children, *July*, 34  
  
 DEFECATION, influence of indigestible residue on, *Sept.*, 453  
 Dehydration fever in children, *July*, 47  
 Dercum's syndrome, *Sept.*, 374  
 Dermatitis, contact, *Sept.*, 651, 653  
 Diabetes mellitus, borderline, *Sept.*, 346  
     with hypothyroidism, *July*, 279  
 Diaphragmatic pleurisy in children, *July*, 18  
 Diathesis, exudative, *Sept.*, 656  
 Dick antitoxin, *July*, 314  
     test, *July*, 312  
     toxin, *July*, 313  
 Diet in cardiovascular-renal disease, *July*, 214  
     in constipation, *Sept.*, 449  
     in myocardial insufficiency, *Sept.*, 555  
     in uremia, *Sept.*, 529  
 Digestive tract diseases in aged, *July*, 132  
 Digitalis in myocardial insufficiency, *Sept.*, 549  
 Diuretics in myocardial insufficiency, *Sept.*, 553  
     in uremia, *Sept.*, 530  
 Diverticula, esophageal, in aged, *July*, 132  
 Drugs causing fever in children, *July*, 45  
 Duodenal obstruction in newborn, *Sept.*, 621  
 Dwarfism, *Sept.*, 353  
     hypothyroid, *Sept.*, 356  
     Paltauf, *Sept.*, 362  
 Dysentery, amebic, in children, *July*, 24  
     bacillary, in children, *July*, 24  
 Dyspituitarism, postencephalitic, *July*, 229  
 Dystonia, neurovegetative, *July*, 233  
 Dystrophia adiposogenitalis, *Sept.*, 374  
  
 ECTOPIC pregnancy, *July*, 77  
 Eczema, *Sept.*, 651  
 Eczematids, *Sept.*, 654  
 Edema, cerebral, in newborn, *July*, 105, 109

- Emphysema, early diagnosis and treatment, *Sept.*, 437
- Empyema, *July*, 329
- encapsulated, in children, *July*, 18
- Encephalitis, clinical types, diagnosis and treatment, *Sept.*, 415
- epidemic, *Sept.*, 419
- dyspituitarism following, *July*, 229
- parkinsonism following, diagnosis and treatment, *July*, 223
- in children, *July*, 39
- toxic, *Sept.*, 415
- postvaccinal, *Sept.*, 430
- Encephalomyelitis, acute disseminated, associated with infections, *Sept.*, 430
- Endocarditis, subacute bacterial, in children, *July*, 57
- Endocervicitis, chronic, treatment, *July*, 119
- Endocrine disturbances, borderline, *Sept.*, 337
- in aged, *July*, 138
- infantilism, diagnosis and treatment, *Sept.*, 353
- obesity, *Sept.*, 369
- symposium, *Sept.*, 335
- Enterospasm, infantile, classification and treatment, *Sept.*, 511
- Enuresis and hypothyroidism, *Sept.*, 339
- Epididymitis, gonorrheal, *July*, 150
- Erysipelas in aged, *July*, 137
- Esophagus, obstruction, in newborn, *Sept.*, 617
- pressure, diverticula, in aged, *July*, 132
- Estrogenic hormone therapy in gonorrheal vaginitis, *Sept.*, 669, 675
- Exanthem subitum, *July*, 48
- Exercise in cardiac conditions, *July*, 191
- Exophthalmic goiter, *July*, 285
- Extrasystoles, *July*, 177; *Sept.*, 540
- Exudative diathesis, *Sept.*, 656
- FAINTING, attacks and hypothyroidism, *Sept.*, 339
- Feeding, infant, in relation to vomiting in newborn, *Sept.*, 616
- Fevers in childhood, obscure origin, symposium on, *July*, 1
- Fibro-adenoma of breast, *Sept.*, 633
- Fibromyxoma of breast, *Sept.*, 636
- Iloradex in gonorrheal vaginitis, *Sept.*, 674
- folliculitis, gonorrheal, *July*, 153
- food poisoning in children, *July*, 27
- Food residue, indigestible, influence on defecation, *Sept.*, 453
- method of isolating, *Sept.*, 450
- necessity in diet, *Sept.*, 455
- Foods, bulky, laxative value, *Sept.*, 449
- Foreign body in lung, pulmonary bleeding in, *Sept.*, 488
- Fractures in aged, *July*, 138
- Fröhlich's syndrome, *Sept.*, 374
- Functional disorders of children, diagnosis and treatment, *Sept.*, 581
- Fungus infections of lung, pulmonary bleeding in, *Sept.*, 488
- Fusospirochetosis of lung, pulmonary bleeding in, *Sept.*, 488
- GALLBLADDER, stoneless, diagnosis, *Sept.*, 471
- strawberry, *Sept.*, 473
- Gallstones in aged, *July*, 134
- Gangrene of lung, pulmonary bleeding in, *Sept.*, 487
- Gastro-enterospasm, infantile, classification and treatment, *Sept.*, 511
- Gastro-intestinal obstruction as cause of vomiting in newborn, *Sept.*, 617
- Genetic aspects of certain blood-system disorders, *Sept.*, 253
- Genito-urinary system, diseases, in aged, *July*, 134
- Geriatrics, *July*, 127
- German measles, encephalitis in, *Sept.*, 433
- Gigantism, *Sept.*, 387
- Glandular fever in children, *July*, 55
- Goiter, toxic, *July*, 285
- Gonorrhea in male, complications, treatment, *July*, 147
- Gonorrheal arthritis, *July*, 152
- prostatitis, *July*, 150, 161
- vulvovaginitis, *July*, 123; *Sept.*, 665
- Graves' disease, *July*, 285
- Grippe, intestinal, *July*, 26
- Growth hormone therapy, *Sept.*, 365
- Gynecology, diagnostic mistakes, *July*, 75
- problems of family physician, symposium on, *July*, 59
- HABIT vomiting in newborn, *Sept.*, 624
- Heart, alternation of, *July*, 188; *Sept.*, 545
- block, *July*, 185
- and hypothyroidism, *Sept.*, 339
- disease, in aged, *July*, 139
- pulmonary bleeding in, *Sept.*, 489
- physical exercise in, *July*, 191
- with cyanosis in newborn, *July*, 105, 111

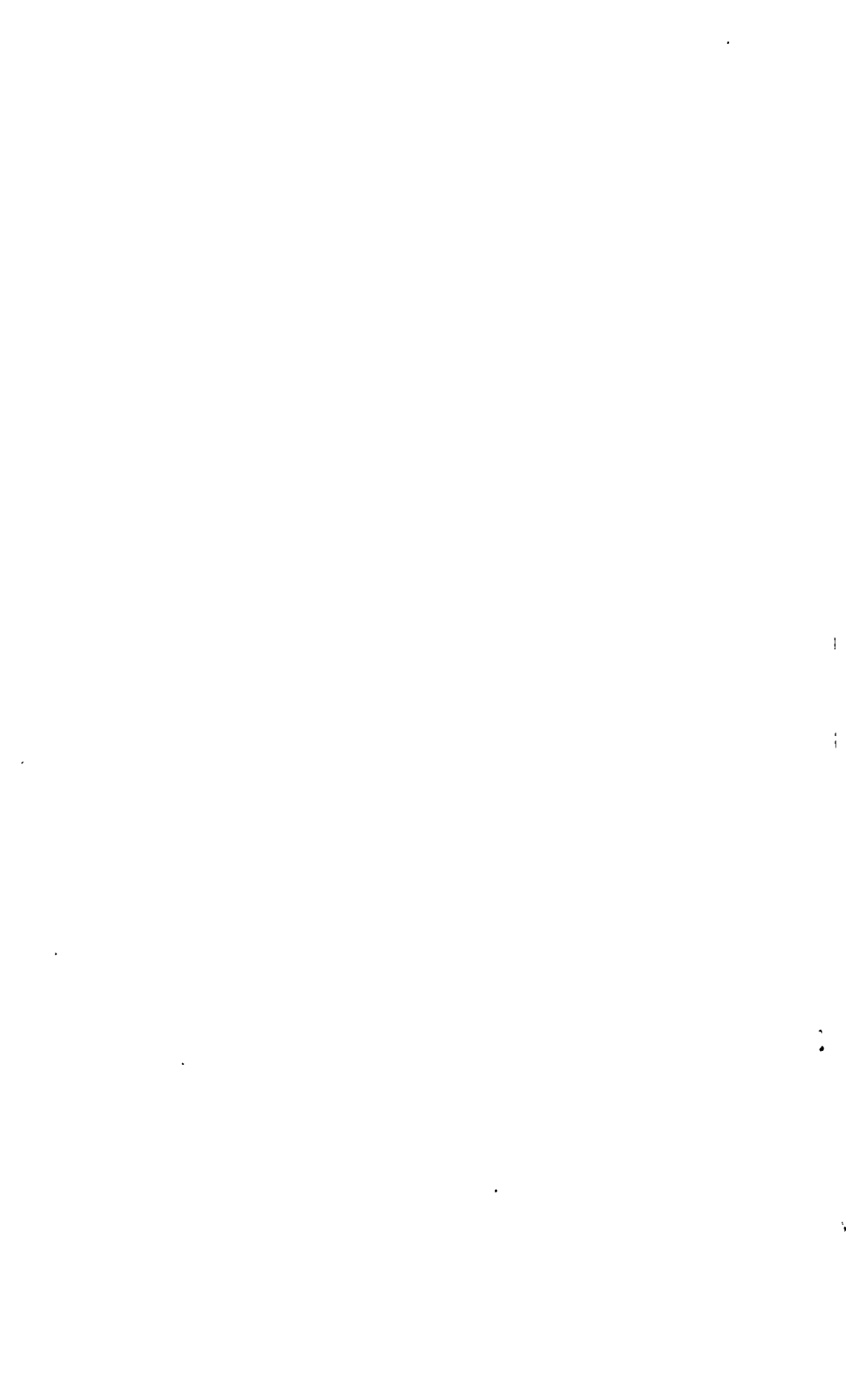
- Heart, irregularities, diagnosis and treatment, *July*, 175  
 significance, *Sept.*, 537  
 premature contractions, *July*, 177  
 Hemicellulose in foods, *Sept.*, 450  
 Hemoglobinuria, paroxysmal, *July*, 56  
 Hemophilia, *July*, 258  
 Hemoptysis, diagnosis and treatment, *Sept.*, 483  
 Hemorrhage, cerebral, in newborn, *July*, 105, 109  
 pulmonary, diagnosis and treatment, *Sept.*, 483  
 Herpes zoster, treatment, *July*, 239  
 Hodgkin's disease in children, *July*, 54  
 Hormone therapy in gonorrheal vaginitis, *Sept.*, 669, 675  
 in habitual abortion, *July*, 96  
 in hypopituitarism, *Sept.*, 384  
 in infantilism, *Sept.*, 360, 364, 365  
 in sterility, *July*, 70  
 Hyperinsulinism, diagnosis and treatment, *Sept.*, 393  
 Hyperpituitarism, treatment, *Sept.*, 386  
 Hypertension in cardiovascular-renal disease, *July*, 209  
 Hyperthyroidism, *July*, 285  
 borderline cases, *Sept.*, 342  
 with normal metabolic rate, *Sept.*, 344  
 Hypoglycemia of hyperinsulinism, *Sept.*, 393, 402  
 differentiation from other states of hypoglycemia, *Sept.*, 404  
 spontaneous, *Sept.*, 347  
 Hypogonadism, primary, *July*, 68  
 Hypopituitarism, treatment, *Sept.*, 379  
 Hypothyroid infantilism, *Sept.*, 356  
 Hypothyroidism, borderline cases, *Sept.*, 337  
 in diabetes mellitus, *July*, 279  
 ICTERO-ANEMIA, hemolytic, genetic aspects, *July*, 256  
 Impedance angle in hyperthyroidism, *July*, 287  
 Infantile colic, classification and treatment, *Sept.*, 511  
 Infantilism, endocrine, diagnosis and treatment, *Sept.*, 353  
 Infections, acute, in aged, *July*, 137  
 encephalitis following, *Sept.*, 430  
 in newborn, vomiting due to, *Sept.*, 622  
 Inflammatory diseases of breast, *Sept.*, 627  
 pelvic, ectopic pregnancy and, differentiation, *July*, 77  
 Influenza, encephalitis following, *Sept.*, 437  
 in children, fever in, *July*, 18  
 Inguinal lymphadenitis in gonorrhea in male, *July*, 156  
 Injuries of lung, pulmonary bleeding in, *Sept.*, 487  
 Intestinal grippe, *July*, 26  
 obstruction in aged, *July*, 133  
 tuberculosis in children, *July*, 21  
 Iodine, blood, in hyperthyroidism, *July*, 286  
 Irritability and hypothyroidism, *Sept.*, 339  
 JAPANESE type B encephalitis, *Sept.*, 423  
 Jaundice, epidemic, in children, *July*, 29  
 KIDNEY, abscesses, multiple, in children, *July*, 33  
 carbuncle, in children, *July*, 33  
 tuberculosis, in children, *July*, 34  
 tumors, in children, *July*, 34  
 LEAD encephalitis, *Sept.*, 417  
 Leukemia in children, *July*, 54  
 Lethargic encephalitis, *Sept.*, 419  
 Lignin in foods, *Sept.*, 450  
 Lipomatosis, *Sept.*, 378  
 Liver, enlargement, diseases associated with, diagnosis, *July*, 295  
 Lobectomy in pulmonary hemorrhage, *Sept.*, 492  
 Lorain-Levi infantilism, *Sept.*, 362  
 Lung, abscesses, multiple, in children, *July*, 18  
 hemorrhage from, diagnosis and treatment, *Sept.*, 483  
 diseases, in aged, *July*, 135  
 Luxus consumption, *Sept.*, 365  
 Lymph nodes, mesenteric, tuberculosis of, *July*, 22  
 Lymphadenitis, cervical, as cause of fever in children, *July*, 14  
 inguinal, in gonorrhea in male, *July*, 156  
 Lymphangitis, gonorrheal, in male, *July*, 156  
 MALARIA in children, *July*, 53  
 inoculata, *July*, 53  
 Malpositions of uterus, diagnostic mistakes, *July*, 79  
 Malta fever, *July*, 51

- Mastitis, cystic, chronic, *Sept.*, 637, 641  
   pyogenic, acute, *Sept.*, 627  
   chronic, *Sept.*, 630  
   tuberculous, *Sept.*, 630  
 Mastoiditis as cause of fever, *July*, 15  
 Measles, encephalitis in, *Sept.*, 432  
 Mediastinal abscess in children, *July*, 19  
   infection, as cause of fever in children, *July*, 18  
 Meningitis, acute aseptic, *July*, 41  
   lymphocytic, *July*, 40  
   serous, *Sept.*, 438  
   meningococcic, *July*, 35  
   miscellaneous forms, *July*, 38  
   syphilitic, *July*, 42  
   tuberculous, *July*, 37  
 Menopause, abnormal bleeding before and after, causes, *July*, 83  
 Menstruation, vicarious, from lungs, *Sept.*, 490  
 Mesenteric lymph nodes, tuberculosis of, *July*, 22  
 Metabolism, basal, in hyperthyroidism, *July*, 288  
 Miscarriage, diagnostic mistakes in, *July*, 76  
   persistent, *July*, 81  
 Mönckeberg's sclerosis, *July*, 130  
 Mononucleosis, acute infectious, *July*, 55  
 Morbus coeruleus, *July*, 106  
 Mumps, encephalitis in, *Sept.*, 436  
 Muscular pains and hypothyroidism, *Sept.*, 340  
 Myocardial insufficiency, treatment, *Sept.*, 547  
 Myxoma, intracanalicular, of breast, *Sept.*, 636  
  
 NANOSOMIA hypothyrotica, *Sept.*, 361  
 Nasal septum, ulcer of, and hypothyroidism, *Sept.*, 338  
 Neoarsphenamine in herpes zoster, *July*, 248  
 Nephrosclerosis in aged, *July*, 134  
 Neurocirculatory asthenia simulating hyperthyroidism, *Sept.*, 343  
 Neuroses from general practitioner's viewpoint, *Sept.*, 559  
 Newborn, cyanosis of, *July*, 99  
   sepsis of, *July*, 47  
   vomiting in, *Sept.*, 615  
  
 OBESITY and hypothyroidism, *Sept.*, 339  
   endocrine, *Sept.*, 369  
   exogenous, *Sept.*, 376  
  
 Obstetric problem of family physician, symposium on, *July*, 59  
 Occupational therapy in myocardial insufficiency, *Sept.*, 557  
 Oculogyric crises, *July*, 228; *Sept.*, 422  
 Oertel terrain exercises, *July*, 203  
 Old age, diseases of, *July*, 127, 131  
 Ornsteen's triad, *July*, 234  
 Osteomyelitis in children, *July*, 49  
 Otitis media, fever due to, *July*, 15  
 Ovalocytosis, *July*, 257  
 Ovarian failure, primary, *July*, 68  
  
 PAGET's disease in aged, *July*, 138  
 Paltauf dwarfism, *Sept.*, 362  
 Pancreatitis, acute, in children, *July*, 26  
 Parafrenal sinusitis in gonorrhea, *July*, 158  
 Paraphimosis, gonorrheal, *July*, 157  
 Paratyphoid fever in children, *July*, 23  
 Parkinsonism, *Sept.*, 422  
   incipient, diagnosis and treatment, *July*, 223  
 Paroxysmal tachycardia, *Sept.*, 544  
 Parrot fever, *July*, 56  
 Pastia's sign, *July*, 309  
 Patch tests in eczema, *Sept.*, 659  
 Pel-Ebstein Hodgkin's disease, *July*, 54  
 Pelvic inflammatory disease, ectopic pregnancy and, differentiation, *July*, 77  
 Peptic ulcer, *Sept.*, 461  
 Perinephric abscess in children, *July*, 33  
 Peritonitis in children, fever in, *July*, 25  
   tuberculous, in children, *July*, 22  
 Pertussis, encephalitis in, *Sept.*, 436  
 Phenobarbital in infantile colic, *Sept.*, 517, 522  
 Phimosis, inflammatory, in gonorrhea, *July*, 156  
 Phlebitis, dorsal, gonorrheal, *July*, 156  
 Phrenic nerve injury in newborn, *July*, 105, 110  
 Phyone, *Sept.*, 360, 364, 384  
 Physical exercise in cardiac conditions, *July*, 191  
 Pill-rolling tremor, *July*, 232  
 Pituitary basophilism, *Sept.*, 349, 387  
   hyperfunction, treatment, *Sept.*, 379  
   infantilism, *Sept.*, 362  
   insufficiency in sterility, *July*, 67  
   treatment, *Sept.*, 379  
 Pituitrin in herpes zoster, *July*, 246  
 Pleurisy, acute, treatment, *July*, 323  
   diaphragmatic, in children, *July*, 18

- Pneumoconiosis, pulmonary bleeding in, *Sept.*, 488  
 Pneumonectomy in pulmonary hemorrhage, *Sept.*, 492  
 Pneumonia in aged, *July*, 136  
     in children, fever in, *July*, 17  
     pulmonary bleeding in, *Sept.*, 488  
 Pneumothorax, artificial, in pulmonary hemorrhage, *Sept.*, 492  
 Poliomyelitis, *July*, 38  
 Postmenopausal bleeding, causes, *July* 88  
 Postural emphysema, *Sept.*, 442  
 Pregnancy, and hypertension, *July*, 221  
     ectopic, pelvic inflammatory disease and, differentiation, *July*, 77  
 Premenopausal bleeding, causes, *July*, 85  
 Prephysis, *Sept.*, 386  
 Prostatic hypertrophy, *July*, 135  
 Prostatitis, chronic, management, *July*, 161  
     foci of infection in, *July*, 168  
     gonorrheal, *July*, 150, 161  
 Pruritus in uremia, treatment, *Sept.*, 533  
 Psittacosis, *July*, 56  
 Psychoses from general practitioner's viewpoint, *Sept.*, 559  
     in aged, *July*, 140  
 Pulsus alternans, *July*, 188  
 Purpura in children, *July*, 57  
 Pyelitis in children, fever due to, *July*, 31  
 Pyloric obstruction in newborn, *Sept.*, 618  
 Pyridium therapy in gonorrheal vaginitis, *Sept.*, 672  
 Pyuria in children, fever due to, *July*, 31  
  
 RABIES inoculations, encephalitis following, *Sept.*, 435  
 Rat-bite fever, *July*, 52  
 Relapsing fever, *July*, 53  
 Renal-cardiovascular disease, preventive aspects, *July*, 209  
 Respiratory disorders in parkinsonism, *July*, 229  
     infections, encephalitis following, *Sept.*, 437  
         lower, in children, fever due to, *July*, 17  
         upper, in children, fever due to, *July*, 9  
 Retropharyngeal abscess as cause of fever in children, *July*, 13  
 Rheumatic fever in children, *July*, 27, 50  
  
 Riedel's lobe, *July*, 299  
 Rocky Mountain spotted fever, *July*, 52  
 Roentgen diagnosis of silicosis, *Sept.*, 505  
     of stoneless gallbladder, *Sept.*, 474  
     treatment, of herpes zoster, *July*, 244  
 Roseola infantum, *July*, 48  
 Rumpel-Leede's sign, *July*, 309  
  
 SCARLET FEVER, *July*, 307  
 Schultz-Charlton reaction, *July*, 315  
 Sclerosis, Mönckeberg's, *July*, 130  
 Scurvy in children, *July*, 49  
 Seminal vesiculitis in gonorrhea, *July*, 154  
 Senescence, changes of, *July*, 128  
 Sepsis of newborn, *July*, 47  
 Sickleemia, *July*, 55  
     genetic aspects, *July*, 258  
 Silicosis, diagnosis and prevention *Sept.*, 497  
 Simmonds' disease, *Sept.*, 383  
 Sinus arrhythmia, *Sept.*, 540  
     infection, paranasal, fever due to, *July*, 11  
 Sinusitis, parafrenal, in gonorrhea, *July*, 158  
 Smallpox, encephalitis in, *Sept.*, 433  
 Sodium iodide in herpes zoster, *July*, 247  
 Spherocytes, *July*, 256  
 Splenomegaly, diseases associated with, diagnosis, *July*, 295  
 St. Louis type encephalitis, *Sept.*, 424  
 Stenosis, pyloric, in newborn, *Sept.*, 618  
 Sterility in female, *July*, 63  
     in male, *July*, 61  
 Stokes-Oertel terrain exercises, *July*, 203  
 Strawberry gallbladder, *Sept.*, 473  
 Subphrenic abscess in children, *July*, 26  
 Syphilitic meningitis in children, *July*, 42  
  
 TACHYCARDIA, paroxysmal, *July*, 179; *Sept.*, 544  
 Teeth, abscessed, in children, *July*, 48  
 Teething, fever due to, *July*, 48  
 Telangiectasia, hereditary hemorrhagic, *July*, 257  
 Tetany in newborn, *July*, 112  
 Thoracentesis in pleurisy, *July*, 328  
 Thymus enlargement in newborn, *July*, 107, 111  
 Thyroid eczema, *Sept.*, 657

- Thyrototoxicosis, hypoglycemia with, *Sept.*, 405
- Tonsils, infected, and fever, *July*, 10
- Trauma in production of eczema, *Sept.*, 653
- Tremor, pill-rolling, *July*, 232
- Trichomonas vaginalis vaginitis, treatment, *July*, 125
- Tuberculosis, intestinal, in children, *July*, 21
- of kidney in children, *July*, 34
- of mesenteric lymph nodes, *July*, 22
- pulmonary, in aged, *July*, 136
- in children, *July*, 19
- pulmonary bleeding in, *Sept.*, 485
- Tuberculous mastitis, *Sept.*, 630
- meningitis in children, *July*, 37
- peritonitis in children, *July*, 22
- Tularemia, *July*, 51
- Tumors, adrenal cortical, *Sept.*, 349
- of brain in children, *July*, 46
- of breast, *Sept.*, 633
- of kidney in children, *July*, 34
- Typhoid fever in children, *July*, 23
- Typhus fever, *July*, 52
- ULCER of nasal septum and hypothyroidism, *Sept.*, 338
- peptic, *Sept.*, 461
- Undulant fever in children, *July*, 51
- Uremia, treatment, *Sept.*, 527
- Urethritis, gonorrheal, in male, *July*, 147
- Uterus, malpositions, diagnostic mistakes, *July*, 79
- VACCINATION, encephalitis following, *Sept.*, 430, 433
- Vaginal bleeding, abnormal, pre- and postmenopausal, causes, *July*, 83
- discharges, diagnosing, *July*, 80
- Vaginitis, gonorrheal, treatment, *July*, 123; *Sept.*, 665
- Vagotonia, hypoglycemia in, *Sept.*, 404
- Vascular disease, hypertensive, *July*, 209
- Vesiculitis, seminal, in gonorrhea, *July*, 154
- Vicarious menstruation from lungs, *Sept.*, 490
- Vomiting in newborn, *Sept.*, 615
- uremic, treatment, *Sept.*, 534
- Von Economo encephalitis, *Sept.*, 419
- Von Gierke's disease, infantilism in, *Sept.*, 355
- Vulvovaginitis, different types, treatment, *July*, 122
- gonorrheal, treatment, *Sept.*, 665
- WEIL's disease, *July*, 29
- Whooping cough, encephalitis in, *Sept.*, 436
- YEAST vulvovaginitis, treatment, *July*, 124
- ZOSTER ophthalmicus, *July*, 240
- oticus, *July*, 240





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# CONTENTS

	PAGE
<b>SYMPOSIUM ON PULMONARY TUBERCULOSIS</b>	
<b>The Pathology and Pathogenesis of Pulmonary Tuberculosis</b> .....	689
By DR. OSCAR AUERBACH	
<b>Tuberculosis in Childhood</b> .....	719
By DR. BÉLA SCHICK	
<b>Clinical Forms of Pulmonary Tuberculosis: Their Recognition and Treatment</b> .....	737
By DR. DAVID ULMAR	
<b>Hematogenous Tuberculosis of the Lungs</b> .....	759
By DR. DAVID REISNER	
<b>Management of Far Advanced Tuberculosis</b> .....	775
By DR. GEORGE G. ORNSTEIN	
<b>Urogenital Tuberculosis Associated with Pulmonary Tuberculosis</b> .....	787
By DRS. ARTHUR J. GREENBERGER and MONROE E. GREENBERGER	
<b>Pregnancy and Tuberculosis</b> .....	811
By DR. M. KOVNAT	
<b>Fluoroscopy and x-Ray in Pneumothorax Therapy</b> .....	819
By DR. I. G. EPSTEIN	
<b>The Treatment of Diabetes Complicated by Tuberculosis</b> .....	829
By DR. S. EDWARD KING	
<b>Tuberculous Empyema</b> .....	841
By DR. RALPH F. HARLOW	
<b>Gastro-Intestinal Symptoms in Pulmonary Tuberculosis</b> .....	851
By DRS. IRVING GRAY and IRVING GREENFIELD	
<b>A New Conception of the Mechanics and Physiology of Cough</b> .....	861
By DR. POL N. CORYLLOS	
<b>Diet Prescription for the Tuberculous</b> .....	877
By DR. MILTON A. BRIDGES	
<b>Chronic Constipation</b> .....	891
By DR. WALTER A. BASTEDO	
<b>Asthma: Treatment by Intratracheal Injection of Iodized Oil</b> .....	907
By DR. M. JOSEPH MANDELBAUM	
<b>Management of Nutritional Anemia in Infancy</b> .....	933
By DR. CARL H. SMITH	
<b>The Care and Feeding of the Premature Infant: With Special Reference to Simple Milk Mixtures</b> .....	951
By DR. ABRAHAM TOW	
<b>The Management of Rheumatic Heart Disease</b> .....	961
By DR. LUCY PORTER SUTTON	
<b>Some Clinical Aspects of Periarthritis Nodosa</b> .....	973
By DRS. LINN J. BOYD and CARL NUSSBAUM	
<b>The Hormonal Treatment of Acne Vulgaris</b> .....	985
By DR. THEODORE ROSENTHAL	
<b>Tuberculodermis</b> .....	995
By DRS. MARION B. SULZBERGER and JOSEPH GOODMAN	
<b>The Diagnosis of Malignancy of the Urinary Tract</b> .....	1009
By DR. A. HYMAN	
<b>Common Urologic Conditions in Children</b> .....	1027
By DR. MEREDITH F. CAMPBELL	
<b>Index to Volume 20</b> .....	1041

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# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON PULMONARY TUBERCULOSIS

The following clinics are included in this Symposium:

Oscar Auerbach: THE PATHOLOGY AND PATHOGENESIS OF PULMONARY TUBERCULOSIS.

Bela Schick: TUBERCULOSIS IN CHILDHOOD.

David Ulmar: CLINICAL FORMS OF PULMONARY TUBERCULOSIS: THEIR RECOGNITION AND TREATMENT.

David Reisner: HEMATogenous TUBERCULOSIS OF THE LUNGS.

George G. Ornstein: MANAGEMENT OF FAR ADVANCED TUBERCULOSIS.

Arthur J. Greenberger and Monroe E. Greenberger: UROGENITAL TUBERCULOSIS ASSOCIATED WITH PULMONARY TUBERCULOSIS.

M. Kovnat: PREGNANCY AND TUBERCULOSIS.

I. G. Epstein: FLUOROSCOPY AND x-RAY IN PNEUMOTHORAX THERAPY.

S. Edward King: THE TREATMENT OF DIABETES COMPLICATED BY TUBERCULOSIS.

Ralph F. Harloe: TUBERCULOUS EMPYEMA.

Irving Gray and Irving Greenfield: GASTRO-INTESTINAL SYMPTOMS IN PULMONARY TUBERCULOSIS.

Pol N. Coryllos: A NEW CONCEPTION OF THE MECHANICS AND PHYSIOLOGY OF COUGH.

Milton A. Bridges: DIET PRESCRIPTION FOR THE TUBERCULOUS.



## CLINIC OF DR. OSCAR AUERBACH

FROM THE DEPARTMENT OF PATHOLOGY, SEA VIEW HOSPITAL

### THE PATHOLOGY AND PATHOGENESIS OF PULMONARY TUBERCULOSIS

IN recent years roentgenologic findings have added so much to our knowledge of tuberculosis that pathology must be re-evaluated.

Ranke<sup>1</sup> divided tuberculosis into three stages analogous to those of syphilis. He termed the primary complex the first stage; the period of generalization the second stage, and isolated organ tuberculosis the third stage. All stages are related to allergic phenomena: the first stage is tuberculosis in an uninfected body; the second is tuberculosis in an oversensitized body; and the third stage is tuberculosis in a relatively immune body.

The chief objection to this view is that, although the stages in syphilis are sharply differentiated chronologically and in distribution, and pathologically show the changes of a single original infection, the total disease picture in tuberculosis has never been demonstrated to result similarly from a single infection. Moreover, the origin of the third stage is still debatable. Undoubtedly many cases of isolated pulmonary tuberculosis do not pass through a stage of generalization, but arise as a result of an exogenous infection.

**The Primary Complex.**—The tuberculous infection which begins as a nodular formation at the site of its entry into the body, with a similar involvement of the regional lymph nodes, was designated by Ranke as the primary complex. In most



cases the primary complex runs a definite course with definite anatomical healing. The correspondence of the anatomical changes within the focus and its draining lymph nodes distinguishes the primary complex from reinfects. Remnants of the primary complex, so frequently found at postmortem, represent the oldest tuberculous changes in the body.

*Site and Frequency.*—It is generally agreed that about 80 per cent of foci are found in the lungs. Fewer foci are found in chronic pulmonary tuberculosis because of the presence of excavations. Long and careful search is often necessary in order to demonstrate the remnants of a primary complex. The incidence of extrapulmonary primary infections, as reported, is variable, the greatest number occurring in the gastro-intestinal tract. The incidence of primary intestinal tuberculosis varies from 1.8 per cent (Puhl)<sup>2</sup> to 32.7 per cent (Blacklock).<sup>3</sup> One can rely upon calcified mesenteric lymph nodes, usually in the ileocecal region, as evidence of a healed intestinal primary complex. The intestinal primary infection is attributed to the bovine type of tubercle bacillus, which generally enters in the region of the terminal ileum. According to Huebschmann<sup>4</sup> and Jaffe,<sup>5</sup> a small ulcer in this region heals quickly without leaving a scar. Huebschmann believes, also, that the tubercle bacilli may pass through the wall into the mesenteric lymph nodes without causing disease in the intestines. It is not altogether correct to designate a calcified node as evidence of primary infection, for, as Jaffe has pointed out, nonspecific infection may result in calcification of the mesenteric nodes. In a few cases both primary pulmonary and primary intestinal tuberculosis are observed. Cases of primary tuberculosis of the skin, tonsils, and middle ear have also been described.

**Pulmonary Primary Focus.**—The pulmonary primary focus, as a rule, occurs in early childhood, the greatest number of recent foci being seen in the first three years of life. Huebschmann reports that 60 per cent of fresh foci occur up to the age of fifteen years.

*Site.*—The foci are present chiefly in the well aerated

portions of the lung. This is readily understood when one considers that the focus is the result of the aspiration of tubercle bacilli. Ghon<sup>6</sup> and Puhl<sup>2</sup> found the foci more frequently in the upper lobes, whereas Küss,<sup>7</sup> Hedren<sup>8</sup> and Huebschmann<sup>4</sup> found them more often in the lower lobes. We have never seen primary foci in the apical aspects of the upper lobes, but have found them chiefly in the lower parts of the lower lobes. The right lung contains the focus as frequently as does the left, these foci being chiefly in the subpleural region where there is thickening and retraction of the overlying pleura.

*Number of Foci.*—In most instances, there is a single focus, although there may be multiple foci in one or more lobes. These may occur simultaneously, or as reinfects soon after the formation of the original primary focus. (Huebschmann asks whether foci which occur after the original infection may be called primary lesions.) The determination as to whether multiple primary foci occur at one time or at different periods is possible only when the foci are fresh. When anatomical healing is complete, it is no longer possible to ascertain the age of the individual nodules.

*Gross Appearance.*—The size and appearance of the primary focus depends upon the stage of development in which it is found. It may vary from 1 mm. to 2 cm. In the later stages, encapsulation and contraction cause shrinking. The pulmonary focus always remains smaller than the draining lymph nodes—this discrepancy in size being more marked in early than in late stages.

The first stage of primary foci has been observed only rarely. Those authors who have described it saw a localized area of pneumonia. From the rarity with which this pneumonia is observed, there is no doubt that it rapidly undergoes caseation.

The earliest stage of the primary focus usually observed at autopsy is that of an irregularly demarcated area of caseation surrounded by a gray-white capsule. The lung tissue immediately encircling the nodule is pneumonic in character.

When the nodule lies just beneath the pleura a localized fibrinous pleuritis is seen. At this period, the size of the focus varies from 1 to 2 cm. and it is round or polygonal.

In subsequent stages, the focus is surrounded by a definite gray capsule and is well demarcated from surrounding lung tissue. The nodule is circular in outline, and the lung tissue surrounding it is well aerated and sometimes emphysematous.



Fig. 40.—Healed primary complex. The picture shows a calcified focus in the left upper lobe. The lymph nodes in the left superior and left inferior tracheobronchial zone show corresponding changes.

Calcium deposition occurs early in these foci. The first signs of this are seen after encapsulation has become distinct, and consist in fine white points within the caseation. This calcium deposition may continue until the entire focus is composed of a crumbly, white mass surrounded by a gray capsule. When cut with a knife the foci are gritty. The size of the focus now is 1 cm. or less (Fig. 40).

*Microscopic Findings of the Primary Focus.*—Ghon<sup>o</sup> and Zarff,<sup>\*</sup> who described the early appearance of the focus, found an alveolus-filling process. The alveoli contain an exudate composed of polymorphonuclear leukocytes, lymphocytes, fibrin, and alveolar phagocytes. Numerous acid-fast bacilli are present in this pneumonic zone.

The pneumonia rapidly undergoes necrosis and it is usually in this stage of development that the early primary focus is first observed at autopsy. Swollen fibrin, necrotic nuclear remnants, intact polymorphonuclear leukocytes, and lymphocytes, are often seen in the early stages of caseation. The elastic fibers of the alveolar septa, vessels and bronchioles remain intact within the necrotic zone and are demonstrable in the zone of caseation even after calcification and ossification have been established. The presence of intact elastic fibers of the alveolar septa within the caseation identifies the focus as an original area of caseous pneumonia. The elastic fibers are destroyed only when the granulation tissue invades the area of caseation. The area of necrosis is surrounded by a zone of avascular epithelioid cell and giant cell tissue, containing fibroblasts and collagen fibrils. The cells are disposed radially along the inner border and tangentially on the outer aspect. The epithelioid cells may be arranged in tubercle formation along the edge of the caseation.

Beyond this specific granulation tissue, the alveoli contain an exudate (perifocal inflammation), composed of serum, alveolar phagocytes and lymphocytes. The extent of the perifocal inflammation depends upon the size of the caseous focus which it surrounds. The microscopic picture corresponds to the irregularly demarcated area of caseation surrounded by the pneumonic zone observed on gross examination.

As the area ages, the collagen fibrils laid down by the epithelioid cells become thicker and more numerous. They become hyalinized so that a definite capsule is formed. As this hyalinized capsule progresses, there is a simultaneous diminution of the epithelioid and giant cells owing to compression by collagen fibrils. Giant cells persist longer than epithelioid cells.

When the capsule is completely formed, the focus shrinks. The nodule is now spherical in shape. This hyalinized connective tissue is called the specific capsule because of its origin from specific granulation tissue (epithelioid and giant cells).

Surrounding this connective tissue zone there is a loose connective tissue layer which Aschoff has designated a nonspecific capsule. This capsule, which arises from the organization of a perifocal inflammation, is thin, and contains lymphocytes as well as a few compressed alveoli. Since this zone of perifocal inflammation is not extensive, the nonspecific capsule is thin. As a result of the shrinking of the focus there is a stretching of the surrounding alveolar septa, resulting in emphysema.

The caseous areas of the primary complex tend to become calcified. Calcium is deposited within the caseation either in irregular masses or in fine strands which run parallel to the capsule, the latter being designated Liesegang's rings. Calcium, which is deposited early, first appears as fine purple stippling and may be very difficult to differentiate from necrotic nuclear remnants.

The process of bone formation, which occurs with great frequency in the

primary foci, extends over a long period of time and is usually observed in older individuals. Two processes occur together: resorption of calcium and the building of bone spicules. From various parts of the specific capsule there is a proliferation inward of a vascular granulation tissue which resorbs the calcium and, at the same time, forms bony bands. A bony shell is laid down along the inner edge of the capsule and extends outward to replace it. Between the bony trabeculae there is fatty and lymphoid bone marrow.

Calcification and ossification are not the only ultimate fates of the primary focus. Huebschmann<sup>4</sup> believes that the calcium may be completely resorbed without bone deposition. The focus may also be entirely replaced by connective tissue.



Fig. 41.—Progressive primary complex. The primary focus in the basal portion of the left lung is enlarged and caseous. The corresponding peribronchial tracheobronchial lymph nodes are enlarged and caseous.

**Progressive Primary Focus.**—Fortunately for the human race the vast majority of primary foci go on to anatomical healing. Only a small number of cases react differently. Those cases of progressive primary foci that we have observed occurred early in childhood, usually in the first two years of life. Roentgenologically, a progressive enlargement of the focus was demonstrable. The enlarged focus underwent

central liquefaction and was followed by a bronchogenic dissemination (Fig. 41).

The gross appearance of the cavity in the lungs is that of an irregular shaggy excavation lined by soft cheesy masses. Studded throughout both lungs are large caseous nodules, sublobular and lobular in size. Some of these may also

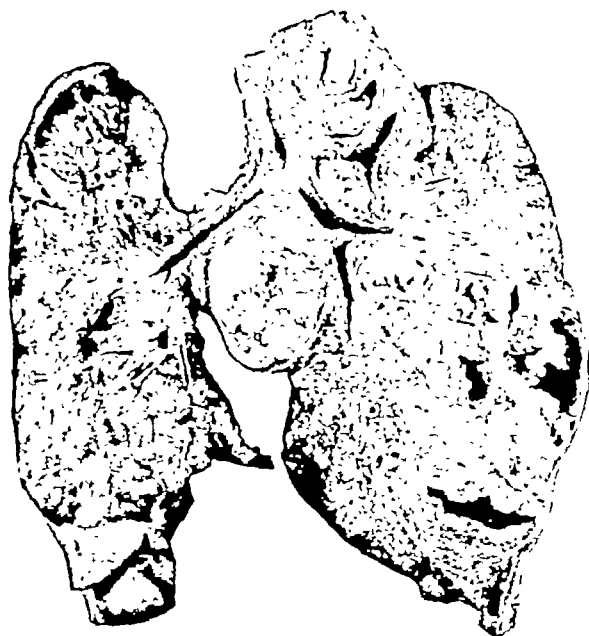


Fig. 42—Progressive primary complex in the stage of liquefaction. The primary focus in the right lower lobe is greatly enlarged and has undergone liquefaction. The corresponding right inferior and right superior tracheo-bronchial lymph nodes also show softening and liquefaction. The remaining lung tissue in the right lung and the entire left lung is studded with large areas of caseous pneumonia. These caseous foci are part bronchogenic in origin and part hematogenous.

undergo liquefaction and cavity formation. Strikingly characteristic are the regional lymph nodes. They are extensively enlarged and caseous and often show central liquefaction similar to that seen in the focus. The corresponding changes in the focus and its draining lymph nodes identify the primary complex during progression, as well in anatomic healing.

Microscopic examination of the primary cavity reveals a scarcity of encapsulation. The sublobular and lobular areas are characterized by the lack of productive reaction at their peripheries.

The extensive caseation of the tracheobronchial lymph nodes indicates an overwhelming infection in the lymph stream. Autopsy often reveals a large nodular tuberculous dissemination in the parenchymatous organs as well as a tuberculous meningitis. This overwhelming hematogenous dissemination is understandable in view of the extensive pouring of tubercle bacilli from the lymphatic system into the blood stream (Fig. 42).

**The Lymph Nodes of the Primary Complex.**—Afferent and efferent lymphatic systems are present in the lungs (Blacklock).<sup>3</sup> The afferent system extends to the pleura and the efferent system drains into the lymph nodes of the hilus. Pulmonary lymph nodes are present along the course of the bronchi as the lymphatics approach the hilar regions. Those lying in the angle between the trachea and bronchi are the nodes most extensively involved. The superior tracheobronchial nodes are connected with the paratracheal nodes while the inferior tracheobronchial nodes communicate with the mediastinal and, in turn, with the peripancreatic nodes. Thus, the peripancreatic lymph nodes are part of the primary complex. Lymphatic vessels connect the lymph nodes of both hili so that, as the primary complex progresses, caseation may cross over to the nodes in the tracheobronchial region on the opposite side.

**Gross Changes.**—The tuberculous process is one of rapid and total caseation involving the chain of lymph nodes which extends from the focus to the tracheobronchial angle. On cross section the lymph nodes, which are greatly enlarged, are dry, caseous, and surrounded by a well defined, thin gray capsule. Those within the lung are smaller than those of the tracheobronchial region, since the pulmonary lymph nodes are normally smaller than those outside the lung. The location of the focus is indicated by the region of most extensive in-

involvement of the tracheobronchial lymph nodes. Thus, if the right inferior tracheobronchial nodes are most involved, the primary focus is usually in the right lower lobe.

Anatomic healing of the lymph nodes, characteristic of the primary complex, is similar to that of the focus. All of the lymph nodes in the chain, however, do not progress to calcification. Those within the lung shrink and are replaced by fibrous tissue.

One of the caseous peribronchial or tracheobronchial lymph nodes of the primary complex may soften and rupture into a bronchus, causing an aspiration caseous pneumonia and cavitation. A node may also rupture into a blood vessel and cause an hematogenous dissemination.

*Microscopic Picture of the Lymph Nodes.*—In the early stage, there is extensive homogenous caseation of the entire node. The formation of specific granulation tissue surrounding the area of caseation, capsule formation, calcium deposition, shrinkage of the node, and ossification occur in the same manner as has been described in the primary focus. Ossification, however, occurs much less frequently in the lymph nodes than it does in the primary focus.

**The Stage of Generalization.**—*Early generalization* corresponds to the second stage of Ranke. It is tuberculosis developing in the oversensitive body, and may be manifested in various forms. There may be a miliary seeding throughout the lung or the nodules may be sublobular and lobular—large nodular tuberculosis. The large nodular seeding occurs in early childhood, and the majority of these cases coming to autopsy show a tuberculous meningitis with multiple tuberculomata of the brain.

*Gross Appearance.*—The lungs are voluminous and on section reveal sublobular and lobular yellow areas of caseation which fuse irregularly with the surrounding pneumonic infiltration (perifocal inflammation). Some authors (Jaffe<sup>5</sup> and Huebschmann<sup>4</sup>) have described a central liquefaction of certain of the foci. Liquefaction of some of these areas will add a bronchogenic factor to an hematogenous spread (Fig. 43).

*Microscopic Findings of Early Generalization.*—Examination of the yellow areas reveals a caseous pneumonia in which elastic fibers of the involved lung



parenchyma are, for the most part, still intact. There is little evidence of reparative activity in the form of productive reaction at the periphery of these caseous areas. The perifocal reaction, however, is extensive, the alveoli adjacent to the caseous foci containing a serocellular exudate. The sublobular and lobular areas are no different from those seen in chronic pulmonary tuberculosis.

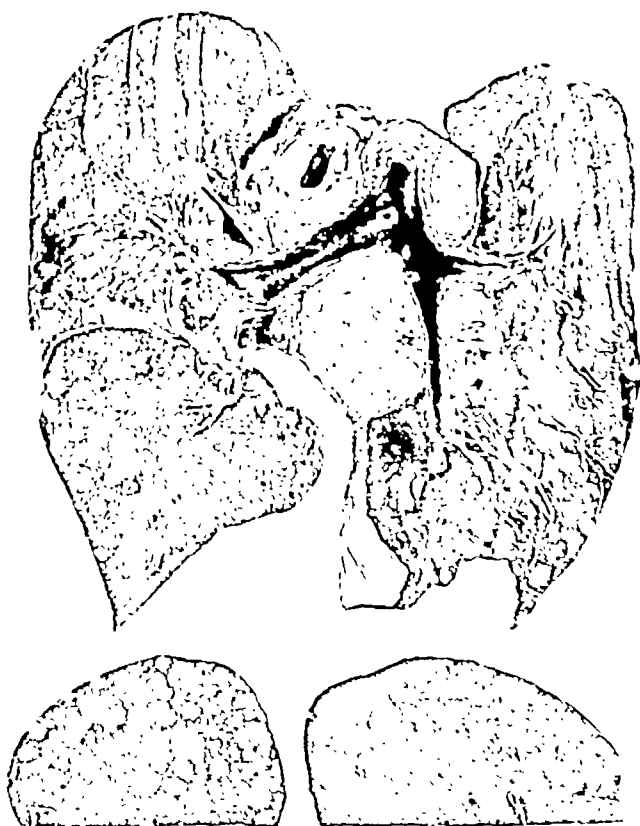


Fig. 43.—Early generalization. Caseous nodules of various sizes are present throughout both lungs. The tracheobronchial lymph nodes are enlarged and caseous. The enlarged nodular dissemination followed soon after the primary complex.

*Late generalization* is the type of dissemination known as generalized miliary tuberculosis because, in the great majority of cases, the nodules approach the size of millet seed (1 mm.). It occurs in adult life and is present most frequently in cases of extrapulmonary tuberculosis, particularly in skeletal and

genito-urinary tuberculosis (Reisner<sup>10</sup>). Pagel<sup>11</sup> and Huebschmann<sup>4</sup> consider that the presence of progressing tuberculosis of a single organ excludes miliary tuberculosis, but Jaffe<sup>5</sup> disagrees because in 20 per cent of his cases of miliary tuberculosis, chronic pulmonary tuberculosis was also present.

Generalized miliary tuberculosis has a varied pathogenesis. Benda<sup>12</sup> describes a tuberculous periphlebitis which occurs through the extension of a tuberculous organ focus into a vein. The caseous focus—usually a lymph node—ruptures into a vein and, in this manner, leads to a generalized miliary tuberculosis. This type of dissemination, which is rare, presents an even seeding throughout all organs. The tubercles are of the same age and size. Intimal tubercles, as described by Weigert,<sup>13</sup> are more frequently observed. The areas of caseation which surround the veins extend into the wall of the vessel and form the intimal tubercles or tuberculous endophlebitis, found most frequently in small lung veins. In form and appearance, the Weigert polypoid intimal tubercle is similar to a thrombus. Tubercles in the pulmonary veins will result in a seeding in the organs supplied by the greater circulation. Pagel<sup>14</sup> agrees with Weigert<sup>13</sup> that the intimal focus is the source of a generalized miliary tuberculosis.

The views of Weigert<sup>13</sup> are not accepted by Huebschmann,<sup>4</sup> who observed cases of generalization in which the intimal focus could not be found. Although he has observed tuberculous ulceration of a pulmonary vein and thoracic duct with thick layers of tubercle bacilli, the majority of his cases revealed intimal tubercles of the pulmonary veins and thoracic ducts which were no older than the other miliary tubercles, and were certainly incapable of releasing masses of tubercle bacilli into the blood stream. Rich,<sup>15</sup> Pinner and Kasper<sup>16</sup> also believe that there is not a sudden invasion of bacilli from an intimal focus into the blood stream, but rather that there is a lymphatic drainage from an organ focus, and, in turn, an emptying into the venous circulation. They believe that the tubercle bacilli multiply in the blood stream resulting in an hematogenous dissemination. We, too, feel that the occurrence of hematogen-

ous miliary tuberculosis is due to lymphatic drainage from an organ focus and that the foci most frequently encountered are skeletal and genito-urinary.

*Gross Appearance.*—Two forms of miliary tuberculosis of the lung must be differentiated: an acute form, in which death occurs within four weeks after dissemination, and a sub-acute or chronic form in which the disease persists for a longer



Fig. 44.—Late generalization. Both lungs are studded with millet seed nodules. The left pleura is thickened and calcified, and on the inner surface soft cheesy particles are still present.

period. In the acute form, the lungs are voluminous and heavy and the lung substance is studded with irregular flat yellow nodules, up to 2 mm. in size, which fuse irregularly with the surrounding pneumonic tissue. In the subacute or chronic form, the lungs are better aerated and contain gray elevated nodules smaller than those found in the acute form and sharply

the nodules are larger and more numerous in the apical ventral aspect than in the posterior basal aspect (Fig. 44).

*Microscopic Picture of Generalized Tuberculosis.*—In the acute form, the exudative character of the nodules predominates, and the picture is the same as that of sublobular caseous pneumonia, as will be described. The productive reaction in the form of epithelioid cell proliferation is seen only sparsely at the periphery of these areas. These foci are rich in tubercle bacilli. In the sub-acute or chronic form, two types of nodules are seen. One is the typical epithelioid cell tubercle containing one or more Langhans giant cells and surrounded by a dense lymphocyte collection; the other has a central area of caseation surrounded by a wall of epithelioid cells and an occasional giant cell. In the area of caseation the elastic outlines of the former alveoli are often intact, indicating that the process was originally pneumonic in character. The alveoli surrounding the nodules contain little or no exudate.

It is generally believed that cellular epithelioid cell tubercles arise from interstitial tissue. Huebschmann,<sup>4</sup> however, contends that epithelioid cell tubercles are later stages of exudative miliary foci, on the basis of the fact that in cases where the exudative foci predominate, the duration is no longer than four weeks, whereas when the nodules are chiefly productive in character the duration is more than eight weeks. He believes, moreover, that epithelioid and giant cells occur secondarily and may partly or completely replace the area of caseation, or form a zone around the necrotic area. He regards the presence of elastic fibers of the alveolar septa still intact in the caseous zone as conclusive evidence of tubercles originating as exudative foci. Although Pagel<sup>11</sup> concedes that many of the tubercles originate as exudative foci, he maintains that the cellular tubercles are productive from the start.

A miliary dissemination may occasionally be observed in the course of the bronchi and blood vessels. These nodules are free from caseation and are purely productive in character. As the collagen fibrils become thicker and more numerous and the epithelioid and giant cells disappear, concentric nodules of hyalinized connective tissue remain. The perivascular arrangement of the nodules and their loss of specificity as well as the deposition of coal pigment within them make their differentiation from miliary silicosis difficult, a difficulty

stressed by Tesseraux and Olmos.<sup>17</sup> The points of differentiation are that in silicosis the vessel is in the center of the silicotic nodule, no epithelioid and giant cells may be found, and there is a history of exposure to dust.

**Isolated Pulmonary Tuberculosis.**—The development of tuberculosis in one system of the body has been designated as isolated organ tuberculosis and represents the third stage of Ranke's classification. The involvement of the gastrointestinal tract, as well as the trachea, bronchi and larynx, is considered as part of the system of isolated pulmonary tuberculosis, because tuberculosis in these tissues depends upon, and is the result of, tuberculosis in the lungs. This type develops long after the primary complex has healed. The manner in which it develops has divided pathologists into two groups. One group believes that there is an endogenous exacerbation of the primary focus or an apical or subapical focus. The other group attributes the origin to a new exogenous infection. Unfortunately, the origin of chronic pulmonary tuberculosis can be studied only in its early phase; as soon as extensive cavitation is present such observation is no longer possible.

*Endogenous Origin.*—Pagel,<sup>18</sup> Schmincke,<sup>19</sup> Huebschmann<sup>4</sup> and Ghon<sup>20</sup> believe that isolated phthisis originates as an endogenous exacerbation of a primary complex or an apical or subapical focus. Such exacerbation has been observed by Pagel<sup>18</sup> in about 25 per cent of his cases, and most frequently in the age group between 16 and 25. The exacerbation is present more frequently in the glandular portion than in the lung focus. Ghon,<sup>20</sup> Jaffe<sup>5</sup> and others also have found exacerbation of the lymph node component of the primary complex with greater frequency than that of the pulmonary focus. In the lymph node the calcified area is encircled by a fresh area of caseation. In the reactivation of the primary focus, an encircling of the older focus by a fresh area of caseation is much less frequent than is the invasion of an outer portion of the focus by a tuberculous granulation tissue. Isolated pulmonary phthisis is the result of a lymphatic drainage from the exacerbated area with subsequent emptying into the venous

circulation. The seeding will occur first in the apical aspects of the upper lobe and the fresh areas produced become an isolated phthisis.

Many investigators doubt the presence of virulent bacilli in the primary complex. Jaffe,<sup>21</sup> assuming that bone cannot be laid down in the presence of virulent bacilli, points out that the process of ossification is frequently observed in the primary complex. Opie and Aronson<sup>22</sup> have found tubercle bacilli in various parts of the lungs and in lymph nodes free from any tuberculous change.

*Endogenous Origin from Hematogenous Apical Foci.*—

Various types of tuberculous nodules are observed at the apices of the lungs. There are postprimary hematogenous miliary seedings to the apices which, because of lack of progression of the tuberculous process, are abortive tubercles, and have been called by Neumann<sup>23</sup> "miliaris descreta." These areas may change into dense scars—"fibrosa densa"—and the miliary nodules tend to become latent so that there is little likelihood of their reactivation. The scars are seen with greater frequency as puberty is approached. Other postprimary foci seen in the apices of the lungs are small, encapsulated, caseous areas, designated as "Simon<sup>24</sup> foci." These foci occur as early postprimary or intraprimarv seedings. Histologically they do not differ from a primary focus except that they are surrounded by more connective tissue. Unlike the primary focus they have no regional lymph nodes with corresponding anatomical changes, and have a predilection for the apices. Although calcium is often observed within the caseation, ossification is rarely seen. Many authors believe that isolated pulmonary tuberculosis arises from these foci and from the larger, but otherwise similar, subapical Aschoff-Puhl foci. Whether the Aschoff-Puhl foci are endogenous or exogenous in origin is still debated. Puhl,<sup>2</sup> who originally described them, believes that they are exogenous, and Aschoff<sup>25</sup> concurs. Pagel,<sup>14</sup> on the other hand, contends that they are endogenous and are identical with Simon foci. One reason for Pagel's endogenous stand is that the Aschoff-Puhl foci are found three times as

often in generalization forms of tuberculosis as in isolated phthisis. The only actual differences between the Simon and Aschoff-Puhl foci are that the former are smaller and apical in location. The Aschoff-Puhl focus may show bone deposition, which has been described by Puhl<sup>2</sup> in three cases. The reactivation of the Simon-Aschoff-Puhl foci may occur in the same manner as the exacerbation in the primary complex. Pagel<sup>14</sup> has shown that these apical foci lie in changed lung tissue. In this region there is scarring and retraction of the lung apices with widening of the apical bronchus. It is through these dilated small bronchi that the invasion from the exacerbated focus extends into the basal aspects of the lung. This bronchial aspiration is believed by many authors, notably Loeschke,<sup>26</sup> Schuermann,<sup>27</sup> and Huebschmann,<sup>4</sup> to result in early infiltration, which initiates isolated pulmonary tuberculosis.

*Exogenous Origin.*—The theory of exogenous origin has been expounded chiefly by the clinician with the aid of the roentgen examination. It was the observation of the shadow and later cavity formation in the infraclavicular region, noted by Wessler and Jaches,<sup>28</sup> Assmann<sup>29</sup> and others that weakened the theretofore inflexible opinion of pathologists that isolated pulmonary tuberculosis begins in the apices, hence is of endogenous origin. Schuermann<sup>27</sup> and Loeschke<sup>26</sup> believe that the early infiltrate is the result of a bronchial aspiration from an exacerbated apical focus. That many cases are indisputably of exogenous origin is shown by the presence of early infiltrates in the lung in which no apical foci are present, whereas in other cases, where apical foci exist, no evidence of exacerbation is seen. Assmann<sup>29</sup> observed these infiltrates chiefly in the lateral infraclavicular region and concluded that they are found most frequently in individuals who have been in contact with tuberculous patients. He made these observations in a tuberculosis hospital where routine roentgen examinations were done on employees. Although resolution of these foci may occur before the stage of caseation develops, most often they progress to caseation and cavitation. After a cavity is formed, other areas

of caseation and cavitation (daughter cavities) result from aspiration of the liquefied particles containing tubercle bacilli. The early infiltrate in some cases has a more basal location.

*Gross Appearances of Isolated Pulmonary Tuberculosis.—*

A survey of the lungs reveals old cavities in the apical aspects with caseous lobular pneumonia and fresh cavities and acinous

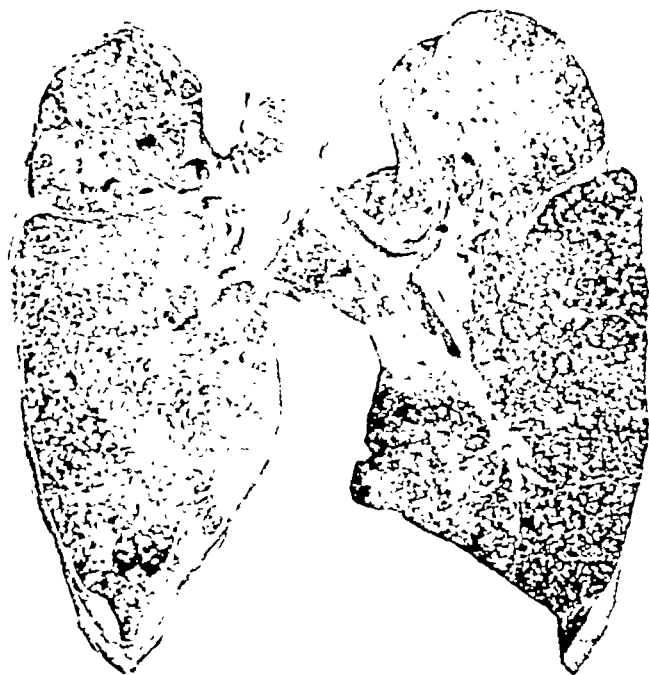


Fig. 45.—Acinous nodose tuberculosis. There is a "tennis racket" excavation in the right upper lobe with a large branch of the right upper lobe bronchus opening into it. The acinous nodose extension involving both lungs evenly is the result of repeated hemorrhages. There is also calcification of the superior tracheobronchial lymph nodes on the right side.

foci in the basal aspect. The apical portion shows evidence of healing in the form of fibrosis and scarring; the basal portion contains the fresher foci in which exudative reaction predominates. Cavities are present in the dorsal and lateral portions of the apical aspects, and may reach such proportions that they occupy the greater part of the upper lobe. Through



roentgenologic study, often with pathological confirmation, Reisner<sup>80</sup> has shown that the oldest cavities are not always present in the upper lobe but may be located in the apical region of the lower lobe. The changes found in both lungs at autopsy may be symmetrical with apical cavities and nodular seedings in the basal aspects; or, one lung may show extensive involvement while the other is relatively free. Hemorrhage markedly affects the disease process, by carrying from the cavities a suspension of tubercle bacilli which is aspirated into other lung parts. The more severe the hemorrhage, the greater the extension into the basal aspect, with predominant large areas of caseation. In the more chronic form acinous nodose involvement dominates the picture (Fig. 45).

The regional lymph nodes are swollen, grayish in color and contain coal pigment in variable amounts. Caseation is seen only in those cases where there is an extensive confluent lobular caseous pneumonia in the lungs, or where there is a generalized lymphatic enlargement throughout the body, with caseation. Caseation of the lymph nodes may occur in the puberty type of tuberculosis described by Aschoff<sup>31</sup> and later elaborated by Beitzke<sup>32</sup>; the nodes are enlarged and caseous but the lungs are similar to those in the adult type. Microscopically, tubercles are invariably found in the glands, with caseation present in their center. Most frequently, however, the tubercles are cellular in character. The lymph sinuses are dilated, a diffuse coal pigment deposition is present and hyalinized connective tissue scars with coal pigment are frequently seen.

The lesions of isolated pulmonary tuberculosis are of two main types: acinous nodose and caseous pneumonic.

**Acinous Nodose Tuberculosis.**—This is a basic type of isolated pulmonary tuberculosis and is characterized by an extensive productive tissue formation.

The acinus, as the anatomic unit of respiration, was first described by Rindfleisch,<sup>33</sup> and comprises the smallest bronchiole with its alveolar ducts and sacs. Opinions vary concerning its point of origin. Obviously, the more proximally the acinus is assumed to originate in the bronchial tree, the

larger will it be. Thus, Loeschke<sup>34</sup> when interpreting the inception of the acinus in the terminal bronchiole reported its size to be 5 mm. But Laguesse<sup>35</sup> and Grethmann<sup>36</sup> hold that the acinus begins with the division of the alveolar ducts and so state that it is approximately 2 mm. in size.

*Gross Appearances.*—Fresh acinous lesions are yellow, somewhat scalloped at the periphery, and are not sharply demarcated from the surrounding firm, pneumonic tissue. In the fresh stage, they are difficult to differentiate from sublobular areas of caseous pneumonia, but older lesions are more characteristic. The nodules have a definite garland-like arrangement at their periphery and are gray in color, but in the central portion of the focus they are black. As the foci grow older, they are composed of radiating scars, and the alveoli surrounding the nodules become dilated (perifocal emphysema), resulting sometimes in large blebs. These blebs may be mistaken for cavities on roentgenological examination. As scarring progresses, the typical scalloped appearance is no longer present.

Acinous nodose foci resulting from fusion of acinous foci, or from extension into neighboring alveoli, still retain the typical appearance of the acinous focus, and are found in two forms, the form providing a clue to mode of origin. One form is composed of a large central area containing a good deal of coal pigment; the periphery, which has a scalloped appearance, is composed of pinhead, pearly, elevated nodules. The individual acinous foci are clearly discernible. If the acinous focus is one large nodule, the method of enlargement is extension into neighboring alveoli, either through bronchioles or through direct extension. In the other form, the acinous nodose focus is the result of fusion of smaller acinous foci with individual nodules still discernible.

Acinous nodose tuberculosis may dominate the pathological picture in isolated pulmonary tuberculosis. When it does, the process is slow with an apicobasal progression. Smaller cavities are present in the apical aspects of the upper lobe. The alveoli surrounding the nodule are dilated. This peri-

focal emphysema results in a marked increase in the volume of the lungs. The condition of the pleura also is strikingly characteristic. Except for the apical regions where the pleura is thickened and adherent it is thin, smooth, glistening, and nonadherent (Auerbach and Guggenheim),<sup>37</sup> which emphasizes the predominantly productive character of the acinous nodose process. The perifocal inflammation which occurs around the exudative caseous foci and reaches the pleura results in its thickening. In acinous and acinous nodose tuberculosis the exudative caseous process is not extensive and productive reaction soon predominates. The roentgenological appearance of this type of tuberculosis is frequently misinterpreted as silicotuberculosis since the symmetrical nodular seeding throughout both lungs simulates silicosis (Ornstein).<sup>38</sup> A questionable history of exposure to dust adds to the difficulty of clinical diagnosis.

*Microscopic Picture of Acinous Nodose Tuberculosis.*—In the majority of cases, the picture is that of an alveolus filling process. In all foci the process is first exudative in character and later productive. This productive character and a slight tendency to liquefaction and cavity formation are clearly seen microscopically. The fresh acinous foci reveal a group of small caseous and cellular nodules, the caseous areas being surrounded by fibroblasts, epithelioid and giant cells. This productive reaction at the periphery of the caseation is pronounced from the beginning. The alveoli about the foci contain serum, large alveolar cells and lymphocytes. This perifocal inflammation is never extensive. The caseous centers may still reveal, in hematoxylin-eosin stain, the outline of the alveolar septa, the elastic fibers being well retained in the early stages. Swollen fibrin, occasional intact polymorphonuclear cells and nuclear remnants may be observed in the necrotic centers.

As the process continues the productive reaction becomes more extensive and may dominate the lesion. The microscopic appearance is that of small round and oval areas of caseation, surrounded by fibrous capsules which take on coal pigment. Many of the productive nodules are composed of concentrically arranged hyalinized connective tissue, and may be the organized cellular foci seen in the fresh stage, or they may be the result of replacement of a central caseous zone by hyalinized connective tissue. With further healing, there is shrinking and scarring of the foci, with an associated dilatation of the surrounding alveoli (perifocal emphysema). Generally there is an interlinking of old and new foci, the new resulting from recent seedings from cavities or by extension of neighboring foci. The surrounding perifocal inflammation is partially organized so that between the individual nodules there is fibrous tissue within which are compressed alveoli lined by metaplastic cuboidal epithelium.

Kaufmann<sup>39</sup> has not accepted acinous nodose tuberculosis as an entity, but, instead, designates this type as tuberculous peribronchitis and contends that the processes are peribronchial and perivascular in nature. Nicol<sup>40</sup> regards the primary process as productive; Huebschmann,<sup>4</sup> in contradistinction, claims it is exudative. Pagel<sup>11</sup> holds that it may be either. In our experience, the evidence favors primary exudative reaction.

Acinous foci are rarely forerunners of cavity formation although they may be drawn into an adjacent liquefying process. A bronchiole or a small bronchus is occasionally observed in the center of an acinous or acinous nodose focus. This bronchiole or bronchus may undergo caseation and subsequent liquefaction, which, by extending into the surrounding focus, may form a cavity.

**Lobular and Lobar Caseous Pneumonia.**—This type of tuberculosis is the forerunner of liquefaction and cavity formation. The involvement is generally lobular, rarely lobar, and, when extensive, is designated "galloping consumption." The massive involvement usually follows severe hemorrhage resulting from rupture of an aneurysm within a cavity. The hemorrhage expels soft, cheesy particles, laden with tubercle bacilli with subsequent aspiration into the lower lobes and the ventral portions of the upper lobes. We have seen extensive caseous pneumonia develop after the installation into a cavity of lipiodol for the purpose of visualizing a bronchial communication with that cavity.

*Gross Appearance.*—In its early stages, the pneumonia is gray or reddish granular in appearance similar to that of any other pneumonia, with yellow areas occasionally present within the consolidation. In its fully developed state, the entire caseous-pneumonic area is yellow and it is flat and indifferently demarcated at the periphery where it fuses with the surrounding firm, flat lung tissue. This perifocal zone is either red or gray and gelatinous in character. Caseous pneumonia may progress to liquefaction and cavity formation, or to encapsulation; if to encapsulation, the greater part of the perifocal inflammation becomes resorbed. Capsule formation and

calcium deposition occur in this process just as in the primary focus.

*Microscopic Appearance of Lobular and Lobar Caseous Pneumonia.*—In the stage before caseation, the alveoli are filled with fibrin, polymorphonuclear leukocytes, red blood cells, lymphocytes and alveolar phagocytes. The presence of tubercle bacilli differentiates this from other pneumonias. As the process continues, the cellular elements undergo necrosis and the fibrin becomes swollen until the end stage, caseation, is reached. The caseous area is pink and granular and within it outlines of alveoli, bronchioles and blood vessels are often still clearly discernible. A relatively mild productive reaction in the form of fibroblasts, epithelioid cells and giant cells is apparent at the periphery of the caseation. The alveoli surrounding the caseous areas contain a serocellular exudate, the cells of which are alveolar phagocytes, lymphocytes and red blood cells. Polymorphonuclear leukocytes are rarely present. In certain areas cells dominate the exudate; in others, serum. When serum is the chief component of the exudate, the term "gelatinous pneumonia" is appropriate since the exudate presents grossly firm, flat, gray, gelatinous tissue.

*Perifocal Inflammation.*—This influences the course of the tuberculous process in the lungs. Its extent parallels the amount of caseation. When the areas of caseation become encapsulated the caseous foci shrink and the greater part of the perifocal inflammation may be eliminated through the bronchi. Should the areas of caseation fail to proceed rapidly to encapsulation and shrinkage, the perifocal inflammation is entrapped, the large caseous zones causing compression of the efferent bronchi so that the exudate cannot be eliminated. There is then a fibroblastic invasion and the exudate may become completely organized, resulting in large areas of fibrosis. Those alveoli which are not replaced by fibrous tissue, are compressed, may or may not contain an exudate, and are lined by metaplastic cuboidal epithelium with a glandular appearance. There is characteristically a thickening of the vessel wall, most marked by an increase of fibrous tissue of the intima encroaching upon the lumen.

**The Tuberculous Cavity.**—This results from the softening and liquefaction of a caseous focus, most often lobular caseous pneumonia. Graeff<sup>41</sup> emphasizes the differentiation between softening and liquefaction. Softening of the caseous

area results from absorption of water whereby the softening focus becomes larger. The process of liquefaction, according to Orth,<sup>42</sup> Aschoff<sup>43</sup> and Schmincke,<sup>44</sup> is due to the action of proteolytic enzymes formed by the polymorphonuclear leukocytes. The important question is, "Under what circumstances do the polymorphonuclear leukocytes enter the area of caseation?" Graeff holds that the migration of these leukocytes depends upon the hydrogen ion concentration of the caseous material and that there must first be an acidity to produce a chemotactic influence on the leukocytes. Liquefaction may occur in one of two ways: in one form, a demarcation zone of polymorphonuclear leukocytes is present between the area of caseation and the healthy lung tissue (Orth);<sup>42</sup> in the second form, the leukocytes encircle and invade the area of caseation. The first type of liquefaction was designated by Schmincke<sup>44</sup> as sequestering, and the latter as an abscess form. A zone of demarcation at the periphery of the caseation develops simultaneously with liquefaction, this zone becoming the inner wall of the cavity as liquefaction is completed.

Cavities may be open or closed. An open cavity communicates with the bronchial tree. It may arise either from liquefaction of a caseous area or from a caseous bronchitis. A closed cavity has no communication with the bronchial tree and arises only from liquefaction of an encapsulated caseous focus. By extension, a closed cavity may become an open one after rupturing into a bronchus or into a neighboring open cavity.

*Gross Appearance.*—The size of the cavity varies from one which may be seen only microscopically to one occupying almost the entire lung. The average size observed at post-mortem is from 7 to 10 cm. Although cavities rarely pass from one lobe into another, it is possible for such giant cavities to occur as a result of the fusion of smaller cavities. On occasion, they have been mistaken roentgenologically for pneumothorax cavities. The location of the cavity is generally in the upper portion of the upper lobe. The first cavities are observed clinically in the infraclavicular region; as they enlarge, they ex-

tend to the apex and occupy the upper parts of the lobe. Smaller cavities are observed in the lower parts of the lower lobe. The form is variable depending upon the circumstances under which it develops. If it results from a caseous pneumonia and lies in previously unchanged lung tissue, its form will be fairly regular, being club-shaped, oval or round. If it develops in an area surrounded by cirrhotic tissue, or if multiple cavities fuse with one another, or if a fresh liquefaction ruptures into an older cavity, irregularly formed cavities result.

After expulsion of the liquefied cheesy material the boundary of the cavity is formed by a capsule. Its inner wall is lined by a thin, dirty gray membrane which may be easily scraped away. Attached to this inner layer, or pyogenic membrane, are soft cheesy particles known as Koch lentils, which are laden with tubercle bacilli. These cheesy particles are numerous in the early stages of cavity formation, but as the cavity progresses they diminish. Beyond the pyogenic membrane is a layer of red tissue forming a narrow zone of vascular granulation tissue. The third layer—beyond the vascular granulation tissue—is firm, flat, gray, and may fuse with the pleura where the cavity is situated superficially. The width of the third layer increases with the age of the cavity. In long-standing cavities there are numerous trabeculae which represent thrombotic pulmonary arteries. Their thickness depends upon the size of the involved vessel. On cross section they have a gray or red appearance and the lumen of the vessel is obliterated.

When the elastic lamellae of the vessels are preserved, slowing of the blood stream, secondary to compression of the vessels, results in thrombosis. Sometimes the caseation quickly extends to the arteries resulting in a destruction of their elastic lamellae with the subsequent formation of aneurysmal dilatation of the vessel (aneurysm of Rasmussen). These aneurysms are situated within the cavity in the region of the inner wall and their rupture usually results in a fatal hemorrhage; the bronchi, cavities and alveoli fill with blood so that death results from suffocation.

*Microscopic Appearance of the Cavity Wall.*—Microscopically, the wall of a cavity varies with its stage of development. The term "finished cavity" is applied when the liquefied material has been expelled and the zone of demarcation is complete. The wall of the great majority of finished cavities is composed of three layers. The innermost zone, designated pyogenic membrane, is made up of a base of thick bands of fibrin containing chiefly intact polymorphonuclear leukocytes as well as fibroblasts and lymphocytes. Beyond this is a zone composed of dilated capillaries which accounts for the red appearance observed macroscopically in the second layer of the cavity wall, *i. e.*, the layer of vascular granulation tissue. Surrounding this is a layer composed of thick fibrous tissue that is poor in blood vessels. The width of this zone depends upon the age of the cavity—the older the cavity, the wider the zone. This third layer arises from the organization of perifocal inflammation around the original caseous pneumonia; as this organization progresses, the width of the layer increases. Although compressed alveoli are seen in the first two layers of the cavity, they are present in greatest number in the third, or fibrous layer.

*Cavity Healing.*—This may occur with or without the closure of the lumen. Huebschmann,<sup>4</sup> Graeff,<sup>44</sup> Tchertkoff and Bobrowitz,<sup>45</sup> and others have described the spontaneous closure of cavities. Huebschmann believes that only cavities the size of a walnut or smaller are capable of spontaneous closure. Closure is the result of the shrinking of the fibrous wall (the vascular granulation tissue having been converted into fibrous tissue) and the filling in of the lumen by granulation tissue. Microscopically the end stage of closure is a ringlike arrangement of fibrous tissue encircling a small slit. At the periphery the fibrous tissue radiates irregularly into the surrounding lung.

The other form of cavity healing may occur in a vomica of any size. The pyogenic membrane is replaced by bands of fibrous tissue, the wall then being composed of hyalinized connective tissue laden with coal pigment. We have observed epithelialization of cavities in two cases. The epithelium lining the cavity was squamous in type and extended onto the trabeculae. Beyond the epithelium was a wide layer of vascular granulation tissue. Here and there, in the cavity wall, an epithelioid-giant cell tubercle was observed.

Cavity healing has been greatly aided by artificial pneumothorax and thoracoplasty. Collapse therapy approximates the



walls of the cavity as well as of the bronchi. The amount of scarring surrounding the cavity is much greater in surgically compressed lungs than in those of nonsurgical cases. The reason for this is the organization of perifocal inflammation which cannot escape through the bronchi because of their compression. This increase in the encircling scar tissue undoubtedly aids in the contraction of the vomica. Backmeister<sup>46</sup> and Coryllos<sup>47</sup> believe that the closure of cavities is preceded

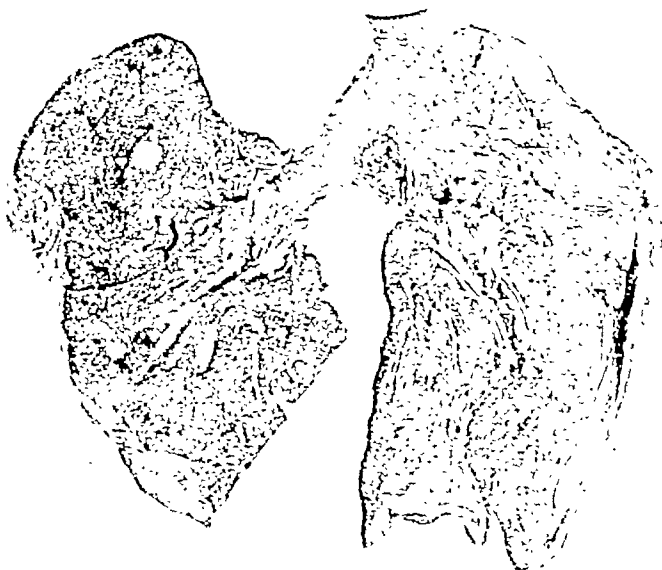


Fig. 46.—Status postthoracoplasty. Note a slitlike excavation in the right upper lobe. Two bronchi leading to this excavation were closed. The right upper lobe is compressed and the pleura overlying it is extensively thickened. There are two Aschoff-Puhl foci in the left lung.

by closure of the bronchi. We have studied at autopsy a few cases in which negative sputum had resulted after artificial pneumothorax; there was an approximation of the walls of a large bronchus opening into the cavity, although the cavity was patent and a probe could be passed from the bronchus into the excavation. It is highly probable that the negative sputum was the result of a functional closure of the bronchus, for, although a probe could be passed through the potential

lumen by pushing aside the approximal walls, sputum could not have so passed.

With continued bronchial compression, granulation tissue of a cavity wall may extend across the obliterated lumen of the bronchus so that the bronchus ends blindly at the cavity wall. Another result of compression of the bronchus by artificial pneumothorax is the proliferation of granulation tissue within the bronchial lumen itself, obliterating the bronchus at its junction with the cavity resulting in a cul-de-sac (Fig. 46).

**Spontaneous Pneumothorax (Tuberculosis).**—Spontaneous pneumothorax and its sequelae must be considered as complications of cavity formation inasmuch as their occurrence is generally the result of perforation of a cavity into the pleural space. These perforations occur when an area of caseous pneumonia extends to the pleura, resulting in a caseous pleuritis. As liquefaction sets in, not only is the pneumonic area involved but also the caseous pleuritis.

Cases complicated by perforation are not so numerous as cases of uncomplicated isolated pulmonary tuberculosis. The reason is that the perifocal inflammation surrounding the caseous pneumonia usually extends to the pleura where it sets up a nonspecific fibrinous pleuritis leading to fibrous tissue formation and an obliteration of the pleural space. The fate of spontaneous pneumothoraces is variable; as a rule, after continuous deflation, the perforation is sealed off by a proliferation of granulation tissue extending inward from all sides of the pleural opening, but this sealing off occurs only in barely perceptible perforations. The result of the spontaneous pneumothorax is a tuberculous effusion into the enlarged pleural space, followed sooner or later by mixed infection. The organisms most frequently found with tubercle bacilli are the streptococci, staphylococci and pneumococci.

**Chronic Hematogenous Tuberculosis.**—Pagel<sup>14</sup> has elaborated upon this form of tuberculous involvement, which must be differentiated from isolated pulmonary tuberculosis. The involvement of the lungs is characterized by a symmetri-

cal nodular seeding, most marked in the apices and decreasing toward the bases. The nodules may appear as acinous foci, and as scarring occurs, the surrounding lung tissue becomes emphysematous. The result is a chronic hematogenous emphysematous tuberculosis. Simon and Aschoff-Puhl foci are seen frequently in this type of dissemination. Typical thin-walled excavations (punched-out cavities) lying in unchanged lung tissue are found in the dorsal and subpleural aspects of the upper lobes. Microscopically these cavity walls reveal a thin zone of vascular granulation tissue, and, beyond this, a narrow layer of connective tissue.

The origin of this type of tuberculosis, according to Pagel,<sup>14</sup> is either from apical foci (Simon, Aschoff-Puhl) or from peripheral organs such as the skeletal system and the genito-urinary tract. The primary complex usually shows no sign of exacerbation. Involvement of the larynx and gastro-intestinal tract occurs in 20 to 35 per cent of cases, whereas in isolated pulmonary tuberculosis these organs are involved in approximately 70 per cent of cases. This is explained by the fact that in isolated phthisis there are large excavations from which tubercle bacilli are expelled. Through expectoration and swallowing these bacilli infect the larynx and the gastro-intestinal tract. In chronic hematogenous dissemination, however, since only small excavations are present and since the process is predominantly productive in character, fewer bacilli are liberated into the larynx and gastro-intestinal tract.

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## CLINIC OF DR. BELA SCHICK

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#### TUBERCULOSIS IN CHILDHOOD

WHEN the tubercle bacillus invades the human organism for the first time, the clinical and pathological pictures of the disease following this invasion show distinct and significant features which are quite different from those seen in a case where the tubercle bacillus attacks an individual previously infected with tuberculosis, whether this attack is brought about by a superinfection from without or within. Since, in the majority of cases, the first invasion of the bacillus occurs during the period of childhood, the generally accepted terminology for the form of tuberculosis observed during childhood is "the childhood type of tuberculosis." By this nomenclature is meant that if an adult is successfully invaded by the tubercular bacillus for the first time he also develops the "childhood type of tuberculosis."

The tubercular infection usually takes place by inhalation of the germs into the lungs. Other ways of infection, as cutaneous, congenital, intestinal, etc., seldom occur. Intestinal infection is usually caused by the ingestion of raw milk containing the bovine type of the bacillus. In the United States where the milk production is rigidly supervised and where the milk is either pasteurized or not used until boiled, the occurrence of intestinal infection is negligible. That such an infection can be easily produced was proved by the tragic accident in Luebeck, Germany, where by mistake, virulent bacilli were fed to newborn children in the attempt to vaccinate these children with the attenuated *Bacillus Calmette-Guérin*.

The gastro-intestinal wall is capable of being permeated by the tubercle bacillus particularly during the first month of life.

The primary effect in tuberculosis is established at the place of entrance of the tubercle bacillus in an alveolus or in a small bronchiolus. It was difficult to find early stages of the disease. A real exudative inflammatory process is established in the form of a pneumonia caused by the tubercle bacilli. The bacilli travel immediately after the infection along the lymphatic vessels to the regional glands. Bronchopulmonary and bronchial glands become infected on the same side where the primary focus is situated. On the lymphatic way the tubercle bacilli proceed further to the regional glands in the bifurcation. Clinically and pathologically the primary focus and its regional glands compose the first stage of the disease—the so-called “primary complex of tuberculosis” (Ranke). Two to three weeks are required to develop symptoms of the first stage that can be microscopically detected, for their clinical manifestation four to six weeks and more may be needed, from the localization of the diseased gland we can infer the situation of the primary forms.

In the majority of cases the primary focus is very small, frequently located subpleurally and is sometimes difficult to detect even microscopically. Usually it is not larger than a pea or bean. According to Ghon's statistics, 174 out of 184 cases had a primary focus smaller than a hazel-nut. Eighty-three were as large as a pea and 27 were as large as a bean. Needless to say one is unable to detect such a small infiltration by percussion or auscultation and even the  $x$ -ray does not always reveal such a small focus as long as it is not calcified. Only in those cases where the primary affection grows by spreading into the surrounding tissues and so forms large exudative infiltrations or later caseous masses or cavities that the diagnosis becomes possible mainly by means of  $x$ -ray examination.

Usually only *one* primary focus is found. Ghon and Winternitz found among 606 cases only 28 (4.62 per cent) with two primary foci. More than two primary foci are still

rarer. Ghon and Kudlich found 18 calcified primary foci in a three-and-one-half-year-old girl. The establishment of the primary focus inhibits the development of new primary foci. Multiple primary foci are apparently only developed during the incubation time of the tuberculous infection. The distribution of the primary focus was, according to Ghon, as follows:

	Per cent.	Per cent.	
R. U. L.....	196	29	The right side is more frequently involved (54 per cent), the right upper more often than the right lower lobe.
L. U. L.....	167	25	
R. L. L.....	126	19	
L. L. L.....	125	19	
R. M. L.....	57	8	

In his classical treatise Ghon failed to find the primary focus only in 0.5 per cent of the 790 cases. In 729 cases (92 per cent), the primary focus was found in the lungs. Only 20 cases (2.5 per cent) showed an extrapulmonary focus, 14 of them in the intestinal tract. Only one case was found where the primary focus was in the right tonsil. The teachings that the tonsils are frequently the portal of entrance of tuberculosis is erroneous.

There are already, during early stages of the infection, animal experiments which prove that the tubercle bacillus proceeds further than the regional lymph nodes. The lymphatic way leads to the ductus thoracicus and further on to the blood circulation. In this way, tubercle bacilli may reach different organs of the body. In most of the cases this advance does not produce any clinical or anatomical signs. Thus the majority of cases develop only to the syndrome of the primary complex. In cases of mild infection or when the organism has a good resistance, the primary focus heals by scar formation, frequently with some calcification. The healing process in the infectious gland is somewhat slower, the inflammatory process leading to caseation and later after many months to shrinkage and calcification. It is an interesting fact that if the primary focus be small, it may heal entirely like the primary lesion of syphilis. In the center of the regional gland one still finds,



even in cases of so-called "complete cure," living tubercle bacilli, the existence and life of which can be proved by their *ability to infect guinea-pigs*. The clinical arrest of the disease requires at least two or three years. The primary focus, which is, as mentioned before, frequently invisible roentgenologically becomes conspicuous on the plate when calcification takes place. It can be easily diagnosed in this stage of incomplete or complete healing by the presence of a definite bone- and projectile-like round shadow at a distance from the hilus. Shadows of enlarged lymph nodes particularly in the hilus and paratracheal region belonging to the primary complex are visible eventually without calcification and become more distinct in the event of calcification.

These radioscopic findings are important, as calcification in other than tubercular processes is very rare. The diagnosis of a previously established tuberculous infection can thus be made.

The further advances of the disease lead to the so-called "secondary stage" which is characterized by the spreading and generalization of the tuberculosis virus. There are four ways of dissemination:

(1) Lymphatic, (2) hematogenous, (3) bronchogenous, (4) enterogenous. I mentioned the fact that even in cases where clinically and anatomically only the primary complex becomes visible one has to assume that tubercle bacilli *travel along the lymphatic way into the venous part of the circulation*. Thus the lymphatic way becomes a hematogenous way. The hematogenous way may be taken by *arrosion of the pulmonic vein by an adjoining tuberculous lymph gland or by arrosion of the innominate vein at the angle near to the vena cava superior*. In the first case, tubercle bacilli reach directly the veins leading to the left heart without having to traverse the entire pulmonic circulation. In the latter case of arrosion of the innominate vein tubercle bacilli arrive first at the right ventricle and can be filtered out into the lung capillaries and reach only the left heart and the large circulation after this filtration. Miliary tuberculosis of the lungs is thus more easily

established and the organs of the larger circulation get smaller amount of tubercle bacilli. In case a pulmonic vein is arroded the entire mass of tubercle bacilli appear in the left ventricle and are thrown into the large circulation. These bacilli may settle down in any organ. The generalization of the tuberculous infection is therefore possible. It is easily understood that the fate of the individual is determined by three factors. First, by the intensity of the invasion; secondly, by the resistance of the individual; thirdly, by the importance of the organ attacked by the bacilli. Invasion by a few tubercle bacilli will certainly occur very frequently but the organism is able to destroy them within the circulation or arrest any localized small damage before they produce clinical symptoms. It may happen that some bacilli which became settled in an organ (brain, kidney, bone, etc.) are only temporarily made innocuous, as long as the resistance of this organ is satisfactory. In case of injury or lowered resistance such dormant foci may gain better foothold and develop symptoms. It is also possible that with lowered general resistance circulating tubercle bacilli are able to obtain more easily localization in an organ. In case of injury circulating bacilli settle down in the region of the tissue damaged by this injury. It seems to be that even many months after the primary focus is established insignificant foci may early disseminated, become manifest and dominate the clinical picture. But it has to be remembered that the primary complex still exists if tuberculous foci (brain, bone, joint, etc.) are scattered far away from it. These foci are secondary (metastatic) foci derived from the primary complex.

If the invasion is a very massive one, miliary tuberculosis of all organs may follow (galloping tuberculosis) with fatal outcome. In case of less massive invasion, it makes a difference in the prognosis what organ is the seat of the tuberculous process. A tuberculous process in a metacarpus bone is less dangerous than a process in the brain or in a vertebra. The breakdown of the tuberculous focus in the metacarpus bone leads to suppuration. In this way the entire tuberculosis focus can be excreted through a fistula. But the tubercle in the

brain leads easily to the development of a tuberculous meningitis, a disease with 100 per cent mortality. At the autopsy of a case of tuberculous meningitis, as a rule, tuberculous foci are found in the brain and along the vessels. Tubercle bacilli liberated from these foci infect the meninges. The tuberculous process in a vertebra is located in the body of the vertebra. This is a dangerous localization, the suppurative process may destroy the continuity of the spinal column or it may extend either toward the medulla compressing it and threatening again the development of a tuberculosis of the central nervous system or it may proceed toward the anterior surface producing a sinking abscess. Long lasting suppuration may produce amyloidosis.

Fortunately the vast majority of cases with tuberculous infection escape the visible settlement of tubercle bacilli and production of metastatic foci in spite of the fact that tubercle bacilli invade the circulation. Löwenstein was able to show that in special culture taken from the blood of individuals with tuberculosis tubercle bacilli grew. These findings have been questioned. Many authors were unable to confirm his statement. A study of cases in Sea View Hospital (Lydia Shapiro) showed only 4 to 5 per cent positive results among progressed cases of tuberculosis. Löwenstein published much higher figures. However, he has more experience in this matter; in his latest publication he points out that he has made 24,000 blood cultures. It must be admitted that a better acquaintance with the method may facilitate a higher percentage of positive results. From clinical viewpoint it seems plausible to accept the results of Löwenstein, because many clinical facts can only be explained on the supposition that tubercle bacilli invade from time to time the circulation. This invasion is most likely not a continuous one but rather an interrupted one: it can be said that there is no continuous dripping or raining of the bacilli into the circulation but the invasion may be compared to a hailstorm of tubercle bacilli lasting for a few hours and a more or less frequent recurrence thereof.

The third way in which the tubercle bacillus can spread is

within the branches of the bronchial tree. Already, in the primary stage the focus of the tuberculous infection readily extends to the neighboring ramifications of the bronchial tree, this increasing the size of the primary infection. The primary affection is in direct connection with the air passage; it is an early form of open tuberculosis. Tubercle bacilli and tuberculous material accumulate in the air passages near the primary affection by coughing and by the normal movement of the bronchial secretion tubercle bacilli reach the more centrally located bronchial ramification. With the following inspirations, such infectious material is readily aspirated to other parts of the same lobe of the lung or in other lobes of the same side. If the tuberculous material is coughed up higher, that is up to the level of the bifurcation, aspiration of this material into the main bronchus of the *other* lung is possible. The dosage must again be considered when determining how much damage will follow such a bronchogenous spread. A small amount may be destroyed without provoking visible alterations. Larger doses will create an inflammatory exudative process at the site of their settlement. The size of this secondary focus is usually much larger than the primary affection. Therefore percussion and auscultation will give more definite signs (dulness, bronchial breath sounds and râles) and the x-ray film will show more or less intensive shadowing. This fact should be remembered in judging its pathology. The large size of the process indicates rather that one is not dealing with a primary focus but with secondary foci established by bronchogenous spread. Massive doses of tuberculous material brought up from destructive tuberculous foci may lead to an intensive disseminated tubercular process. At autopsy, the process is characterized by the so-called "acinous" type of tuberculosis (Aschoff). In some cases the bronchogenous spread is initiated by the breakdown of a tubercular gland next to a bronchus. The tubercular process finally arrodes the bronchus and the content of the liquefied and caseated lymph gland is emptied into the bronchus. From here the material can be aspirated in the same way as described above.

The fact that the primary invasion of the tuberculosis takes place almost always in the lung is therefore a decided disadvantage. This localization entails the danger of bronchogenous spread with all its potentialities. A primary focus in the subcutaneous tissue has the other ways of spread (lymphogenous and hematogenous) open but not the bronchogenous. The latter can only be reached indirectly after a pulmonary focus is established on lymphogenous or hematogenous way. The extrapulmonary primary complex has therefore a somewhat better prognosis. Only the danger of lymphohematogenous spread to miliary tuberculosis or tuberculous meningitis looms over the patient.

The diagnosis of childhood tuberculosis at the time of the primary complex is very difficult and frequently impossible if we rely only upon clinical symptoms. As mentioned before percussion and auscultation reveal nothing as long as the primary focus remains small and this is the case in the great majority of cases. The enlarged lymph nodes are so situated that they escape our usual clinical examination. The value of percussion and auscultation for diagnosis is rather questionable. The "Smith phenomenon" and the "Espine sign" may be of value if the physician trains himself specially for elucidating them. Even then errors are too frequent. The  $x$ -ray examination does not reveal the primary focus in its fresh state so long as it is small. A calcified primary focus means healing and that it is not a recent affair. Only primary foci enlarged by bronchogenous spread may be seen on the film. The  $x$ -ray examination gives a better result in revealing shadows in the hilus region representing the cluster of enlarged lymph nodes. Enlarged lymph nodes can be seen on the  $x$ -ray film if they are situated along the trachea, where they produce a shadow in the form of a date reaching out into the lung field. The bifurcation glands which are regularly involved and sometimes very large are so situated that they cannot be visualized on the film. They lie behind the heart shadow. The oblique exposure does not always improve the visualization. Other clinical signs must call our attention to the possibility of the

diagnosis of tuberculosis in the stage of the primary complex. The general toxic effect of the tuberculous infection is shown in *three important* symptoms: (1) loss of appetite, (2) loss of weight, (3) fever of rather mild or medium intensity. Cough, night sweats may be present but are not conspicuous. During infancy, especially in younger infants, the diagnosis of tuberculosis can be made on account of the presence of enlarged lymph nodes on the trachea or main bronchus of either side. The small lumen of the trachea or of the main bronchus becomes very narrow so that especially the expiration becomes labored. An expiratory grunt resembling asthma is produced. In such cases a peculiarly high-pitched cough, sometimes spasmodic, resembling whooping cough, may develop. These symptoms are very characteristic for enlarged tubercular lymph nodes at the bifurcation. The compression of one main bronchus may lead to an atelectasis of the upper lobe.

The second way of diagnosing the presence of tuberculosis in the primary stage is by examining the stomach content obtained by lavage or by examining the feces for tubercle bacilli. Even though an infant or young child coughs he does not expectorate the sputum but swallows it. Rarely are we able to get sputum for examination before the sixth or seven year of life. The sputum swallowed during the night can be recovered by lavage in the morning before breakfast. Tubercle bacilli are frequently found in this manner. Also the feces may be examined. The third method of diagnosing tuberculosis in the primary stage is by testing with tuberculin, which I shall discuss later.

The second stage of tuberculosis, the stage of generalization (Ranke), is somewhat easier to diagnose. The tuberculous foci appearing in the bones or joints are, for most cases, so conspicuous that they will not be overlooked. Predilections of localization are the phalangeal and metacarpal bones, furthermore, the epiphyseal region of the long bones and the body of the vertebral bones. The epiphyseal affection of the long bones precedes the joint involvement. Knee, elbow, wrist, ankle and hip joints are most frequently the seat of tubercu-

losis. The monarticular involvement and chronicity differentiate them from rheumatism. Pleurisy and peritonitis are also easily detected. Secondary foci within the lung, mostly originating through bronchogenous spread, appear frequently large enough to yield to diagnosis by percussion or auscultation. x-Ray examination of the chest is essential, including pictures taken in an oblique position. Shadows due to infiltration situated behind the heart may be otherwise overlooked. The symptoms of meningitis tuberculosa are, in the beginning, difficult to evaluate. A change in the behavior of the child, headache, vomiting and slowing down of the pulse rate should be watched with the idea in mind of an impending tuberculous meningitis. A symptom of active tuberculosis, very helpful for diagnosis, is the appearance of tuberculous skin lesions. Lichen scrofulosus and tuberculosis cutis verrucosa are very characteristic pictures. Of especial importance are the papulonecrotic tuberculides, which are pathognomonic for active tuberculosis and relatively frequent in children of one to two years of age. In cases of miliary tuberculosis such papulonecrotic tuberculides may be very numerous, resembling somewhat in distribution and appearance chickenpox. Papulonecrotic tuberculides are a very definite proof of an active tuberculous process combined with an invasion of tubercle bacilli into the circulation. An intensive eruption of tuberculides is always an alarming symptom as it demonstrates an intensive invasion. In all cases of secondary localization one must realize that the primary complex within the respiratory tract is still present in active form. It may be that the primary affection has become arrested, but the regional lymph glands are certainly actively involved. It is self-understood that the bone, peritoneum or meninges cannot be the seat of the primary affection; they can only be reached by the way of a lymphogenous or hematogenous spread. Pleurisy may develop in direct continuation of the primary affection as the latter is so frequently situated subpleurally near to the surface. But pleurisy develops in the majority of cases as a secondary manifestation and as a part of generalization.

The peculiar picture of *scrofulosis* is characterized by conjunctivitis, keratitis phlyctenulosa, blepharitis and swelling of the region of the lips, etc.; usually the lymph glands in the submaxillar region are swollen and caseated. The picture is lately less frequently seen in our country. Its significance for the diagnosis of tuberculosis is extremely great. Sometimes only conjunctivitis phlyctenulosa is present and just as valuable for the diagnosis of childhood tuberculosis as a positive tuberculin test. Why certain children with tuberculosis develop the syndrome of *scrofulosis* is not known; an additional factor is necessary to change the regular secondary form of tuberculosis into *scrofulosis*. Certain authors feel that the manifestations of *scrofulosis* are only the peculiar reaction of tubercular children to other infectious agents (staphylococci, streptococci, etc.), other authors remarking about the declining incidence of *scrofulosis* think that the increased intake of vitamins is responsible for the reduction.

Another syndrome is usually a sign of an active tubercular process, that is the *erythema nodosum*. In over 90 per cent of the cases of *erythema nodosum* the presence of active tuberculosis can be ascertained. The appearance of these prominent somewhat tender nodes of different size in the skin over the tibia is so conspicuous that the diagnostic value for tuberculosis cannot be overstated. The eruption is rather an early manifestation of generalization of tuberculosis.

The *x-ray examination* is an almost indispensable help in the diagnosis of tuberculosis of the lung. However, it must be stated that the diagnosis should not be based exclusively on the *x-ray* picture. All other clinical and laboratory measures must be considered. Especially an increased hilus shadow may lead frequently to a wrong interpretation, because the intensity and form of hilus shadows is very difficult to judge. It varies normally in different individuals. One should never forget that the *x-ray* picture shows only shadows and not the nature of the underlying process. Infiltrations in the lung fields may for instance be pneumonic in nature even in a tubercular child.



Next to the x-ray examination testing with tuberculin is one of the most important aids for establishing the diagnosis of tuberculosis. It is today a common knowledge that the cutaneous (Pirquet) or intracutaneous (Mantoux test) application of tuberculin produces at the site of application an inflammatory reaction, if the individual has been previously infected with tubercle bacilli. Individuals entirely free from tuberculosis do not react even to large doses of tuberculin. The positive test is a sign of allergy existing in a tubercular individual. Pirquet, the discoverer of the test bearing his name, used concentrated old tuberculin for the cutaneous test. He constructed a borer for it. In case intracutaneous testing is preferred, high dilution of tuberculin must be administered. In active tuberculosis the sensitiveness to tuberculin is usually very high; 0.1 cc. of 1:10,000 gives already a relatively intensive reaction. In less active cases and arrested cases the sensitiveness to tuberculin may be lessened and 0.1 cc. of 1:2000 is necessary to get a positive reaction. Two to three years after complete arrest of the disease the sensitiveness may be much lower and 0.1 cc. of 1:100 = 1 mg. old tuberculin has to be injected. Occasionally one must use still higher doses. A lower sensitiveness also exists during the first weeks of the disease. The safest way to discover tuberculosis in a child is to perform a Pirquet test (cutaneous test) with concentrated old tuberculin. Only in case the Pirquet test is negative an intracutaneous injection of 0.1 cc. of 1:100 (Mantoux test) may be done. This Mantoux test must be made twenty-two or forty-eight hours after a negative Pirquet test. If more time has elapsed, the Pirquet test must be repeated, before a Mantoux test with 0.1 cc. of 1:100 is performed. The Pirquet test increases eventually the sensitiveness to tuberculin. Other authors prefer not to make the Pirquet test but start immediately with the intracutaneous test (Mantoux) with a dilution of 0.1 cc. of 1:10,000 or 0.1 cc. of 1:2000. If this test is negative the dose of tuberculin must be increased. In my experience the testing with 0.1 cc. of 1:2000 is too large a dose for a case of active tuberculosis in a child. A resulting tempera-

ture rise is frequently seen and this should be avoided. Active cases show regularly positive reaction with 0.1 cc. of 1:30,000; some cases are so sensitive that they react to 0.1 cc. of 1:100,000 and even 0.1 cc. of higher dilution.

The positive Pirquet or Mantoux test proves the existence of a tubercular focus in the body, but not necessarily an active process. In infants and children up to three to four years the positive test can be taken as a sign of a relatively active process, because the tuberculous affection needs at least two to four years until it is arrested. The older the child the less we can rely on the positive test as a sign of an active tuberculosis. Beyond seven or eight years many children of the lower economic strata (25-40 per cent of the children) depending upon difference in exposure show a positive test. In this age period the negative test has more weight for the diagnosis. In case of doubt whether a process is tubercular in nature or not, the *negative* test (intracutaneous 1 mg.) will decide *against* tuberculosis. *It is therefore incorrect to state that the tuberculin test in children over seven to eight years has no value.* In this age period the positive test has to be taken cautiously and be weighed together with all other clinical symptoms, before any decision is made, *whereas the negative test is more decisive than the positive test.*

Lately purified tuberculin is used for diagnostic purposes. The practitioner will do better to use at present old tuberculin, until more experience accumulates in its use.

Rubbing of concentrated tuberculin into the skin (Moro test) and the "patch test" gives also satisfactory results similar to the Pirquet test.

Pirquet taught us that the tuberculous infection leads to allergy against the tubercle bacillus and tuberculin. Allergy means altered reactivity. The organism reacts to the reintroduction of the tubercle bacillus quicker and better than at the time of the first invasion. The positive tuberculin test is an expression of the allergic state. Pirquet and after him many authors saw in the established allergy a basis of improved resistance against superinfection from without or within. The

higher resistance of a tuberculous individual was already demonstrated before Pirquet. The fundamental experiment of Koch showed that a tuberculous guinea-pig superinfected subcutaneously with tubercle bacilli heals this new infection quickly. Lately the statement that a child previously infected with tuberculosis has a better resistance against superinfection was questioned by Rich, Myers and Stuart. These authors pointed out that the intensive sensitiveness against tuberculosis is rather a disadvantage than an advantage for the child reexposed to a superinfection. Although it has to be admitted that a hyperergic state may have occasionally a deleterious effect in case of superinfection, the great majority of cases do not show such a high grade of hyperergic reactivity. Therefore the original idea that the primary complex has a beneficial effect on later in life occurring superinfection must be maintained.

The story of the tuberculous infection is not finished with the first chapter of the primary complex and the second chapter of generalization. I mentioned before that within the first years after infection the appearance of new foci may be anticipated. There is only a certain balance between the virulence of the tubercle bacillus and the allergic defense mechanism of the body. The danger of massive invasion and massive generalization diminishes quickly after the first six or nine months of the tubercular disease have elapsed. The ultimate outcome of the infection can then be judged more easily. We shall know how much exudation or destruction is going on, especially in the lung. If these first six to nine months go by without an intensive lung involvement and without too much generalization or without establishing a meningitis tuberculosa, the defense mechanism will work more effectively and arrest the disease in the vast majority of cases. Of course the patient has to be carefully followed up. It may happen that after a relatively quiescent period in the disease new foci appear within the lung parenchyma. The localization of such foci is frequently in the subclavicular region, sometimes even

in the apical region. We assume that this localization may have been present during the earlier periods of the disease without a development of definite symptoms. Loss of appetite, a moderate cough, slight elevation of temperature, will be the warning signal that some flare up has occurred. Percussion reveals some dulness in the infraclavicular region. Râles may be heard.  $\alpha$ -Ray examination reveals some shadowing in this region. This infraclavicular infiltration can resolve again and the arrest of the disease will be established.

In other cases the infraclavicular or apical lesion will progress and will lead to the "adult type" of tuberculosis described elsewhere in this volume. There are two very interesting facts about this development: (1) it is particularly the prepuberty and puberty period of life which have a decided influence upon the breakdown of the resistance toward the tubercle bacillus, and (2) as these two periods appear in girls earlier than in boys the development of the "adult type" of tuberculosis is seen earlier in girls than in boys; in girls usually between nine and thirteen years of age, in boys two to three years later. The pediatrician has more opportunity to see girls suffering from the "adult type" of tuberculosis. It is our impression that the flare-up of the tubercular process develops from superinfection from within more frequently than from superinfection from without. This question must be settled for the individual. Superinfection from without is certainly very important and should be prevented. The resistance of the individual is only a relative one. Intensive superinfection from without can be just as dangerous as a superinfection from within. Personally I think it is better not to insist on a definite decision as to which form of superinfection is more frequent. Both must be fought off. Keeping up the resistance of the individual is necessary under all circumstances and the removal of an individual with an open tuberculosis in the environment of a child is always imperative. There is no doubt that the repeated exposure to superinfection should be avoided at all times. The intensity of the infection is increased by repeated superinfec-

tion. I believe that the early removal of a case of open tuberculosis from the newly infected child and especially infant, will diminish the amount of infectious material in the preprimary, primary and postprimary stage. I have demonstrated (with Karelitz) that in an acute infectious disease like measles the immediate removal of the diseased child from his siblings facilitates the protection of the latter against measles. Much more convalescent serum is necessary, if one wants to protect such children against measles who are continuously exposed to measles during the incubation time.

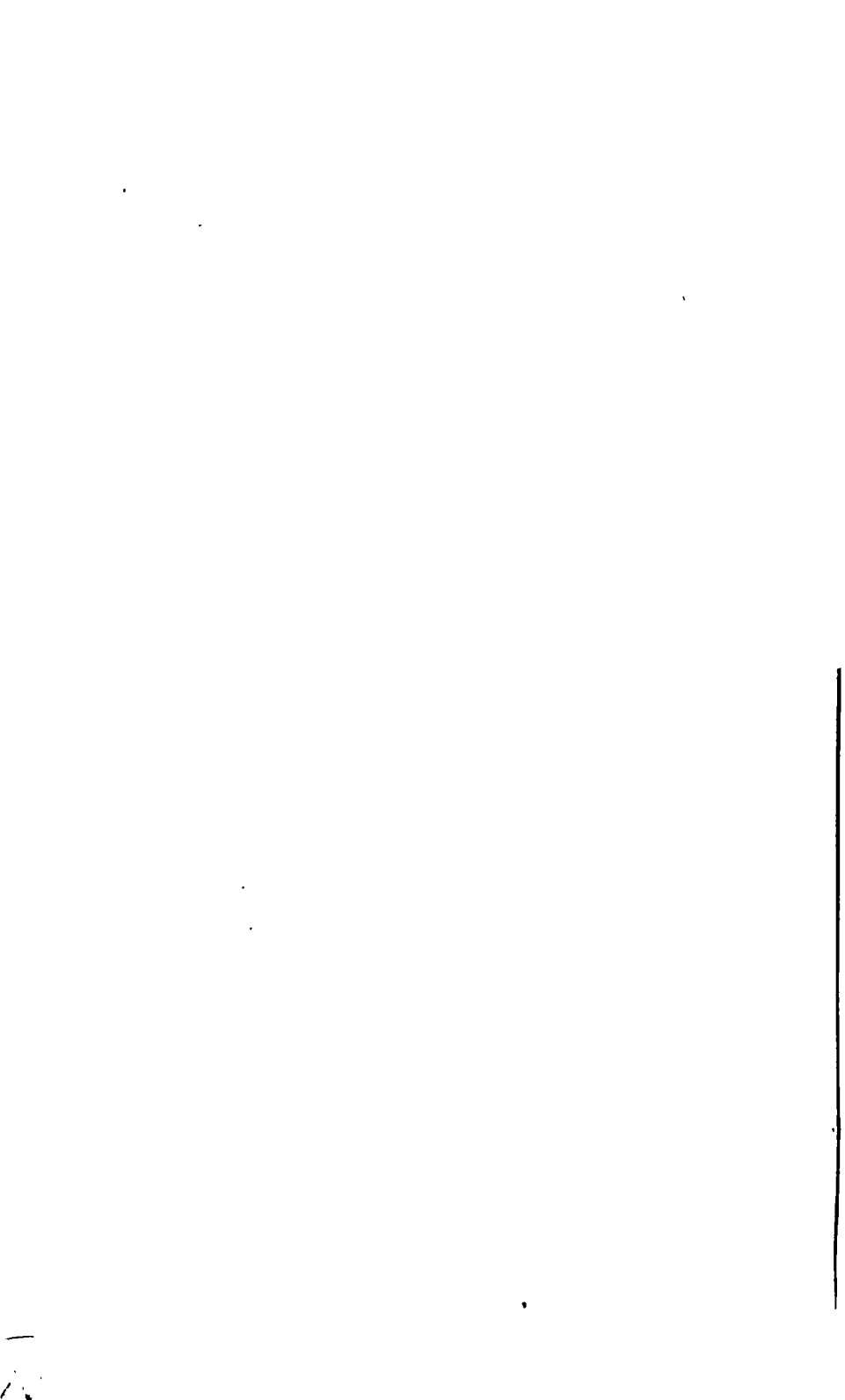
#### PROGNOSIS, PROPHYLAXIS, AND THERAPY

The prognosis of the childhood type of tuberculosis depends upon the age of the child, the intensity of the infection and extension of the disease. The younger the child the greater the danger for massive invasion and therefore for miliary tuberculosis and tubercular meningitis. As mentioned before, the first six to twelve months after the onset of the infection are especially dangerous. The more time which elapses the less frequently does an intensive generalization occur. Destructive processes in the lungs have a bad prognosis in the majority of cases. Destruction leading to cavitation and further to intensive bronchogenous spread progresses very quickly. The cavities are acute cavities; I believe that most of such cases are due to a very massive infection. Disregarding the mentioned danger of massive and repeated exposure the prognosis of a tubercular infection in childhood is far better than was thought before the advent of x-ray examination and tuberculin testing. Whereas before frequently only the violent forms of disease were discovered, we are now able to make the diagnosis much earlier and in individuals who never would have been known to be infected. The incidence of tuberculosis in childhood can be diminished and is greatly diminishing through the intensive battle against tuberculosis in the adult. The discovery of tuberculosis among the parents and other members of the household (servants, maids, visitors, relatives)

and also among teachers must be followed by the removal of the case of open tuberculosis from the environment of the child. The exposure to tuberculosis will be thus delayed until the school age and later, when the infection may be less intensive and the exposure less frequent than within the family. I expect that in this way the incidence of tuberculosis in childhood will be further lowered. The childhood type of tuberculosis shall become more frequent among adults than at present. In order to develop the adult type of tuberculosis one must previously go through the primary complex and the stages afterward. The allergy must be modified until the peculiar reactivity responsible for the adult type is established.

The prophylaxis of tuberculosis in childhood is more important than the therapy. That the tuberculosis of the members of the family must be prevented is clear. In this respect proper food and housing, plenty of sunshine and fresh air, avoiding of overwork are the real measures against tuberculosis. It is evident that our fight against tuberculosis will be incomplete as long as we permit people to live in slums and starve.

The therapy has as its goal the improvement of the resistance. Bed rest, good food, fresh air and sunshine are the most important of therapy for the nonsurgical part of the disease. Lately more attention is paid to a greater supply of all vitamins. Cod liver oil, vitamins C and D, abundance of fresh fruit, fresh vegetables (especially raw vegetables) are recommended. In the last years the pneumothorax treatment even of the postprimary stages of childhood tuberculosis was advocated. I find rarely a case with strict indication. The prepuberty and puberty form of adult type of tuberculosis frequently needs pneumothorax treatment and sometimes thoracoplasty. The results are unfortunately not so satisfactory as in later periods of life. This is mostly due to the fact that the cases come to treatment in an advanced state of the disease. Frequently the process is bilateral. However, we have treated over 90 cases with pneumothorax, some of them with very good results.



## CLINIC OF DR. DAVID ULMAR

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#### CLINICAL FORMS OF PULMONARY TUBERCULOSIS: THEIR RECOGNITION AND TREATMENT

CLINICAL experience with pulmonary tuberculosis has amply demonstrated the fact that all cases of the disease do not react alike. While one patient with extensive pathology recovers rapidly and completely, another individual with seemingly slight pathology may just as rapidly progress to extensive or even fatal outcome. Experiences of this sort at the bedside, with resultant confusion of ideas regarding prognosis and treatment and even diagnosis itself, led to serious thought on the part of some of the workers at the Metropolitan and Sea View Hospitals. Out of the hodge podge and chaos was gradually evolved a clinical classification of pulmonary tuberculosis which has now been in use at these institutions for over six years.<sup>1</sup> Actual trial has fully shown that this classification aids in gauging the prognosis and is invaluable in determining the type of therapy to be performed and in evaluating its results. Its simplicity and ease of application warrant its general adoption.

In order to understand the various types of tuberculous reaction in the lung and to intelligently comprehend their evolution, it is necessary first to keep clearly in mind a few simple but fundamental principles. At birth all individuals are completely free of tubercle bacilli. However, at varying intervals from infancy to adult life, practically all persons, especially those living in urban communities, sooner or later come in contact for the first time, with tubercle bacilli. When these



organisms gain entrance, the usual body defense against bacterial invasion is called into play. There is a slight local reaction at the site of inoculation. Many of the invading organisms, however, escape from this focus and are swept along in the draining lymphatics, to be entrapped by and to multiply in the regional lymph nodes. Even this barrier may not be sufficient to block all of the organisms, although in most instances it does suffice. Nevertheless, not uncommonly a few of the organisms may wander further afield, to be filtered out in the body where they may be. The apices of the lungs are especially good filters and some may be stopped there. Others may reach different parts such as kidney, spleen, bone or what not. This casual and haphazard wandering continues for about ten to fourteen days after the first invasion. At the end of this period, a peculiar change occurs in the tissue of the inoculated individual. One of these changes causes a fixation of the tubercle bacilli wherever they may be, so that henceforth free wandering does not take place. From now on, any similar migration is simply a mechanical accident and not a part of the normal, natural evolution of tubercle. Another tissue change which seems to occur at this same time is an alteration in the sensitivity of the tissue cells to the tubercle bacillus and its products. Whereas formerly the body was not at all sensitive, or allergic, to tubercle bacilli, now it is extremely allergic and reacts violently to minute doses of the tuberculous antigen. The positive tuberculin reaction, which now appears for the first time, is an index of this new sensitivity. In a similar manner, wherever there are deposits of tubercle bacilli in the body this allergic reaction will take place, the most violent reactions, of course, being found where the bacilli are present in the largest numbers. It is, therefore, not unnatural to find a very large zone of inflammation in the regional lymph nodes. Inasmuch as the commonest portal of entry is the lung, the hilum nodes, in such a case, may be tremendously swollen. This condition is sometimes erroneously designated "hilum tuberculosis." It is emphatically not hilum

erculosis, but rather the regional lymph-node involvement in a primary complex whose portal of entry is in the lung. It is not the purpose today to discuss the primary infection, most of which recover without incident. We shall confine ourselves to the reinfection type of pulmonary tuberculosis and the clinical forms which it may assume.

In the reinfection form of tuberculosis, the type that is practically always seen in adults, the inoculation of organisms takes place in a tissue whose reaction has been altered as described above by the previous primary infection. As a result of this change, there is no longer the migration of organisms to the regional lymph nodes. Therefore, they are not grossly enlarged—an important point of differentiation between the primary and reinfected types of infection. But, in addition to this localizing effect, there is also present, as was mentioned before, an increased sensitivity or allergy response, which plays a large part in determining the clinical form of the ensuing tuberculosis. There is considerable variation in the sensitivity of different individuals to tubercle bacilli. Just as some people are sensitive to the pollen of ragweed and, therefore, have hay fever, while others are not—so are some people sensitive to tubercle bacilli, and others relatively less so. Another way of viewing the situation is to state that the threshold level of stimulation of the sensitivity response in the very sensitive individual is low, while in the relatively insensitive individual, it is high. The corollary to this is that the sensitivity response can always be stimulated, provided there is a sufficiently large dose to reach the threshold level. This is exactly what we see clinically. There is, therefore, added another factor, namely, dosage, to the sensitivity response as the predominating influence in determining the clinical form of the ensuing tuberculosis. Depending upon this interplay between allergy and dosage will depend the clinical type of disease.

For the sake of simplicity, the clinical forms of pulmonary tuberculosis may be divided into two main groups: exudative and nonexudative or productive. The exudative forms occur

in the relatively sensitive group of individuals or those who have been subjected to high dosage. The productive forms occur in the relatively insensitive group who have been subjected to small dosage. We shall discuss first the exudative group.

**Benign Exudative Tuberculosis.**—Let us suppose that we have an individual who is very sensitive or allergic to tubercle bacilli and that that individual aspirates a minute quantity of tuberculous antigen. Wherever in the bronchial tree system that this dose lodges there will be produced an immediate violent inflammatory reaction, with an outpouring of serum and fluid in all directions. The broncheolar and alveolar walls will become inflamed and edematous. There

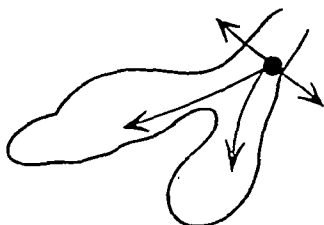


Fig. 47.—From the focal point of inoculation, there has been an inflammatory edema in centrifugal direction.

will be an outpouring of fluid into the alveoli themselves. A glance at Fig. 47 illustrates what has occurred.

The aspirated dose, however, has been small. The pulmonary tissue, while stimulated and irritated, will not be over-irritated to the point of cell death. Therefore, if no further aspiration takes place, the tendency is for a return to normal. The exudation absorbs and normal lung tissue remains.

The clinical picture of this form of tuberculosis, which we can call the benign exudative type, corresponds with our theories of pathogenesis. As can be expected with anyone who is acutely sensitive to allergic stimulation, the patient, after aspiration of the tuberculous material, becomes suddenly ill. There are all the general symptoms of any toxic state such as fever, rapid pulse, malaise and other general symptoms in-

dicative of an acute infection. The severity of these symptoms will depend on the extent of the reaction and may vary from hardly any deviation from normal, as in the case of very minimal lung reaction, to severe prostration, as may be seen with extensive pathology. In addition to these general symptoms, there are also present the localizing symptoms due to the lung irritation. There is a slight cough and slight expectoration. In some instances, there may be actual blood spitting, varying in amount from mere streaking to copious hemorrhage. This latter symptom occurred in 43 per cent of one of our series.<sup>2</sup> Characteristically, however, all symptoms quickly subside, so that within a week or two the patient feels perfectly well and considers that he has recovered from nothing more serious than an ordinary cold.

Physical examination of the lungs does not reveal any startling findings. Possibly there may be slight dulness over the affected part or slightly diminished intensity of breathing. Occasionally there may be heard a fine, high-pitched râle. As often as not the physical signs are apt to be within normal limits. It is only when one fluoroscopes the patient or looks at the x-ray of the chest that one is amazed at the extent of the pathology. Out of all proportion to the scant physical findings or the apparent good health of the patient is seen a more or less homogeneous exudative shadowing of varying size. It may be present in any portion of the lung field, from apex to base. Regardless of its extent, it is quick in its appearance and may disappear almost as quickly. One patient, who had a positive sputum, had complete x-ray clearing in ten days. Usually, however, a longer period is required; two or three months perhaps. Complete clearing of the exudative reaction, as far as can be determined clinically, does occur, so that finally the patient is back to the starting point again. Where the benign exudative reaction was due to an exogenous source, this means that the patient has returned to a normal lung. Where the spill has taken place from some other focus within the lung, this original focus may remain, while the new exudative reaction clears.

Sputum examination, unless done right at the start of the illness, is usually futile for the simple reason that there is no sputum after the first few days. Tubercle bacilli are difficult to demonstrate, but may occasionally be found if diligently searched for at the onset of the disease.

The treatment consists simply of rest and the avoidance of further contact with tubercle bacilli. This means protec-



Fig. 48.—x-Ray of a thirty-year-old woman who complained of right-sided pleurisy three weeks previously. All symptoms had disappeared at the time this picture was snapped. Notice the extensive exudative reaction.

tion from the open case of tuberculosis. All members of the household must be carefully examined, to make sure that the contact is not at home. If the patient is admitted to a sanatorium, it must be remembered that as far as this patient is concerned, tuberculosis is as acute and infectious as is scarlet fever. Isolation procedures should be followed as much as possible. These patients recover if left alone.<sup>3</sup>

I present the following case to illustrate this type of tuberculosis:

B. T., a thirty-year-old female, three weeks before being seen by us had a pleurisy on the right side. She remained in bed two weeks at the end of which time all symptoms had disappeared and the patient returned to work. Because of a rule of the employer's medical department, which automatically referred for consultation any person who, due to pulmonary symptoms, stayed

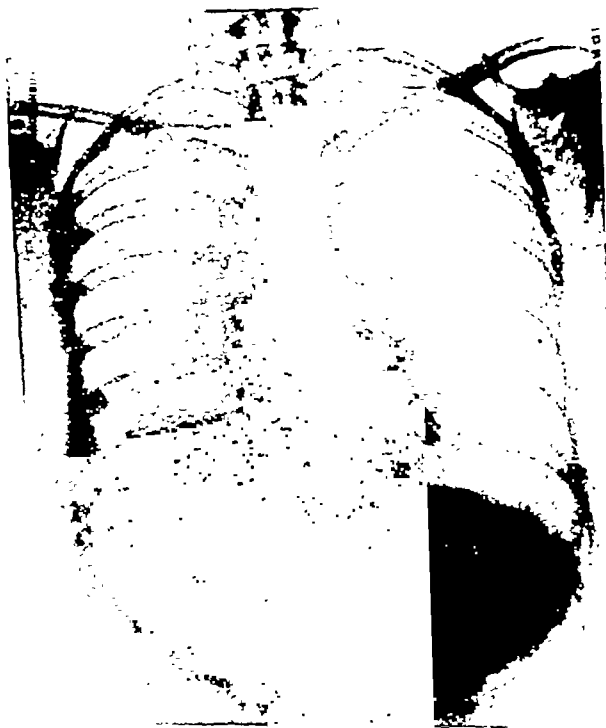


Fig. 49.—Same case as Fig. 48 twenty days later. Note the extensive resolution of the shadowing.

home for three or more days, this girl was seen by us. There were no symptoms whatsoever. The patient's general appearance was excellent. Physical examination of the chest revealed altered breathing over the upper half of the right chest. There was slightly diminished breathing at the right base, with a few fine râles anteriorly.  $\alpha$ -Ray taken at this time is shown in Fig. 48. Notice the extensive shadowing. On nothing more than simple rest, the progress was shown in Fig. 49, taken two months after the original film. She has now returned to work seven months after the original picture was taken.

**Caseous Pneumonic Tuberculosis.**—We have just seen the result where a sensitive individual aspirates a small dose of tuberculous material. Let us now consider the outcome when a large dose is aspirated. Here we have the same allergic stimulation of lung tissue as was seen in the first type. However, because of the large dose of tuberculous antigen, the lung tissue, instead of being merely slightly irritated and stimulated, is overirritated by the excessive allergic stimulation, to the point of cell death. We are now no longer dealing with viable lung tissue, which tends to return to normal, as in the previously described form, but rather with an area of lung gangrene, so to speak, which cannot return to its previous normal state. The whole affair is quite analogous to the Mantoux reaction, where too large a dose is injected and vesiculation or ulceration ensues. Once cell death is established, repair can only take place in the same way as repair occurs following gangrene anywhere else in the body. The necrotic tissue must first be sloughed away, after which the reparative scarring predominates. This is what we also see in the lung that has been overirritated to the point of destruction or caseation. The caseous material is sloughed away and leaves a hole or cavity behind, in place of the previously existing lung tissue. Reparative scar tissue now heals the stump. In other words, the cavity is lined with this scar tissue. As far as that particular phase of the disease is concerned, the patient is cured. Unfortunately for the patient, the scar which lines this cavity is not normal healthy scar, but, usually, tuberculous scar. As we shall see later, this is of most serious import to the patient. This form of exudative tuberculosis, which goes on to caseation and antrum formation, we may designate "caseous pneumonic tuberculosis."

The symptomatology of the patient with caseous pneumonic tuberculosis is quite similar in its onset to the resolving exudative form. Unlike the benign exudative, however, the symptoms of the caseous pneumonic persist. As softening and sloughing of the caseous area takes place, there may be considerable expectoration, which is always loaded with tubercle

bacilli. Gradually, the caseous material is coughed up and expectorated. As this takes place, the expectoration gradually diminishes, although it usually never completely disappears. Characteristically, the sputum in the caseous pneumonic form is always loaded with tubercle bacilli, even after the acute phase has passed. This is so because of the fact that the reparative scar is a tuberculous scar from which there is a constant breaking down of tubercle and shedding of bacilli into the cavity. With the expectoration of the original caseous area, the toxic absorption diminishes so that the patient begins to improve clinically. The temperature gradually subsides, appetite improves, weight gains may be made. The patient may now feel perfectly well again. However, there usually remains slight cough and expectoration. This may sometimes be present only in the morning on arising. As has been said before, tubercle bacilli are always present. It is important to remember that occasionally the true sputum may be unconsciously swallowed, so that no search is complete without examination of the gastric contents for tubercle bacilli.<sup>4</sup> When the patient has reached this point of comparative well being, the chronic end-stage of the acute caseous pneumonic form of pulmonary tuberculosis has been reached. It is important to remember this point. In the past, this later phase of the acute caseous pneumonic form has been confusingly and erroneously called "fibrocaseous"—"fibro-ulcerative"—"fibro-cavernous" tuberculosis. These various so-called "forms" are merely part of the caseous pneumonic type, although seen in a different time phase.

The physical signs of the caseous pneumonic form, in contradistinction to the benign exudative type, are usually plentiful, especially after softening of the caseous area begins. There is alteration of the normal vesicular breathing to bronchovesicular, broncho-amphoric, or other types of breathing, depending upon the underlying pathology. Râles are usually numerous and may be quite coarse in size. Of course, the detection of altered signs will depend upon whether or not



the pathology is available to this method of search. Deep-seated lesions that are surrounded by normal lung may reveal no evidence on physical examination of their presence.

x-Ray examination of the caseous pneumonic form, on single picture, may frequently be confused with the x-ray of the benign exudative form and has led frequently to gross errors in treatment. The film shows more or less extensive zones of exudation, which may occupy any portion of the lung field. Serial pictures show the basic differences in the two forms. While the benign exudative clears by resolution, the caseous pneumonic clears by sloughing and cavity formation, so that the end-stage shows cavity of varying size and scar. With contracture of this scar and perhaps other mechanisms, there is shifting of mediastinum and trachea, such as is seen in no other type of tuberculosis.

As might be expected with a process of this sort, various complications can occur. If the pneumonic process is sudden and extensive enough, there may be symptoms of rather severe anoxemia with cyanosis, breathlessness and other evidence of respiratory failure. If the caseation reaches the pleural surface of the lung and sloughs through before there has been opportunity for an adhesion to form between the visceral and parietal layers of the pleura, a spontaneous pneumothorax and subsequent pyopneumothorax will ensue. The constant expectoration of bacilli and swallowing of some of them may produce a tuberculous involvement of the gastro-intestinal tract. This complication was found in well over 50 per cent of our cases. In a similar fashion the larynx may become involved. By far the greatest complication, however, in the caseous pneumonic form of pulmonary tuberculosis is the probability of bronchogenic extension of the disease. No longer need the patient come in contact with anyone else to contract the illness. By means of his own positive sputum, he is his own contact. From an open cavity, no matter how small, the positive sputum can trickle into other parts of the lung to set up new foci of disease. This most serious complication takes

place, sooner or later, in over 90 per cent of the cases. Its prevention constitutes one of the major problems of treatment.

I shall dwell but briefly on the treatment of the caseous pneumonic form of pulmonary tuberculosis. The treatment phase may be divided into two parts: treatment of the acute stage and treatment of the subacute and chronic stages. During the acute stage, it has been our experience that bed rest and symptomatic treatment give the best result, in addition to avoiding the pitfall of overtreating the benign exudative form, which at first glance might seem similar to the caseous pneumonic form, but which clears spontaneously and without active, outside help.

Once the sloughing out process has occurred and the subacute or chronic stage is reached, the problem becomes a mechanical one of closing off the cavity to obtain a negative sputum. Various procedures are used, all of which depend upon a lung collapse mechanism. Pneumothorax, with various adjuvants, if necessary, such as closed pneumonolysis for the severance of adhesions, may be tried. If pneumothorax is unsuccessful because of adhesions, various plastic operations on the chest wall itself may be done to obtain a collapse of the lung. The success of the treatment is gauged solely by the disappearance of bacilli from the sputum. Where the process is bilateral, as frequently happens, the amount of treatment is limited only by the mechanical skill of the doctor and the physiological capacity of the patient.

I present now the following case, which illustrates the caseous pneumonic form of pulmonary tuberculosis:

V. L., a twenty-one-year-old female, was admitted to one of the municipal hospitals with a pneumonia on the right side. She remained in the institution three months and was then discharged. The initial film is shown in Fig. 50 and her discharge film in Fig. 51. Note the clearing, but also note the residual scarring and the small cavity. The sputum was negative for tubercle bacilli, but gastric examination was not done. The patient worked for one year and felt well. Cough and expectoration then reappeared, along with fatigue and loss of weight. Her new x-ray is shown in Fig. 52. Tubercle bacilli were readily demonstrated in the sputum. The patient went rapidly downhill and died.



Fig. 50.—x-Ray of a young woman showing an exudative pulmonary reaction in the upper lobe on the right.



Fig. 51—Same patient as Fig. 50, but three months later. There has been a clinical recovery and a gain in weight. Considerable resolution has occurred. However, note the annular shadow in the first interspace on the right.

This case illustrates what may happen, and usually does happen, to the caseous pneumonic form of tuberculosis, if the cavity is not closed. General good health and weight gain mean nothing, as long as there are any free bacilli in the bronchial tree. It is important to utilize every means at our disposal before we tell a patient that his sputum is negative.

**Exudative Productive Tuberculosis.**—In addition to the rapidly resolving benign exudative tuberculosis and the malignant exudative or caseous pneumonic tuberculosis, there



Fig. 52.—One year later. Note how there has been a bronchogenic extension of the disease from the small focus in the right apex.

is another clinical type of exudative tuberculosis, which we can term the exudative productive form. In this type, because of the peculiar balance between allergy and dosage, there is produced a form of tuberculosis which is acute and exudative in onset, but in which there is some slight but definite lung destruction. Clearing and resolution of the exudation does occur, but not to the completeness which is seen in the benign exudative. Nor does sloughing and destruction occur to the extent that is seen in the caseous pneumonic group. Rather

is a middle course followed. While extensive resolution takes place, there usually remain some linear strands of scarring in the center of the involved area.

The symptomatology of the exudative productive form follows a similar middle course. The complaints gradually subside; not as quickly as the benign exudative type, but sooner than in the caseous pneumonic form. The sputum, although positive at the start, is never as highly positive as in the caseous pneumonic patient. It soon begins to diminish in amount as well as in bacillary content so that after a few months it may be negative. This is rarely seen normally in the true caseous pneumonic form.

The physical signs correspond roughly to the changes in pathology. At the start, they are not as scant as in the benign exudative type. The altered quality of breathing and moist râles are modified and diminished as resolution progresses. In a similar fashion, the serial x-ray pictures change from extensive, exudative shadowing at the start to a few fibrous strands at the completion of the affair. The whole evolution may last from six to eighteen months.

The following case demonstrates this form of tuberculosis:

V. B., when first seen, gave a history of a chest cold with a productive cough for three weeks and pain in the right chest for one week. On physical examination, there was dulness, harsh tubular breathing and coarse moist râles to the fourth rib. There was a temperature of 102.8° F. and a pulse of 124. Tubercle bacilli were present in the sputum in goodly number. The x-ray appearance at this time is shown in Fig. 53. After seventeen months' sanatorium care all symptoms had disappeared. The sputum was long since negative. There had been a weight gain of almost 50 pounds.

**Chronic Productive Tuberculosis.**—We have just discussed the exudative forms of pulmonary tuberculosis. We now pass on to the productive type. In this category we are probably dealing with an individual of low sensitivity, who aspirates a relatively small dose of tubercle bacilli. The threshold level of stimulation of the sensitivity response is not reached. Therefore, we do not see clinically any of the acute allergic manifestations which predominated in the other forms.

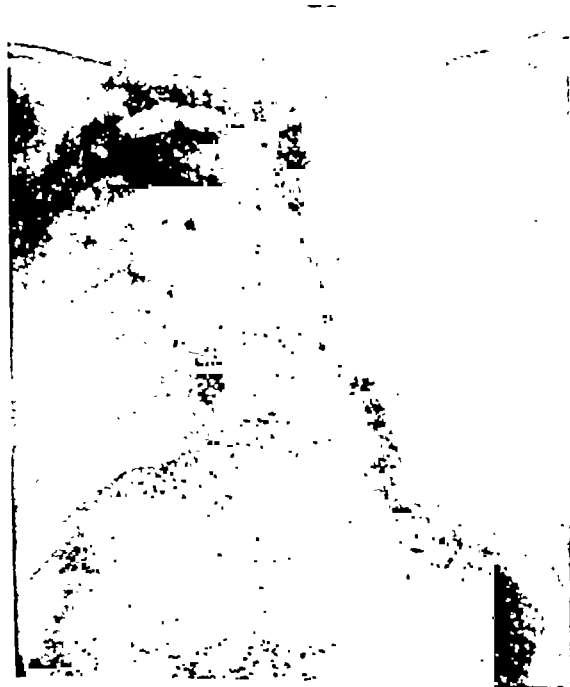


Fig. 53.—x-Ray of a white adult showing the dense exudative shadowing on the right.

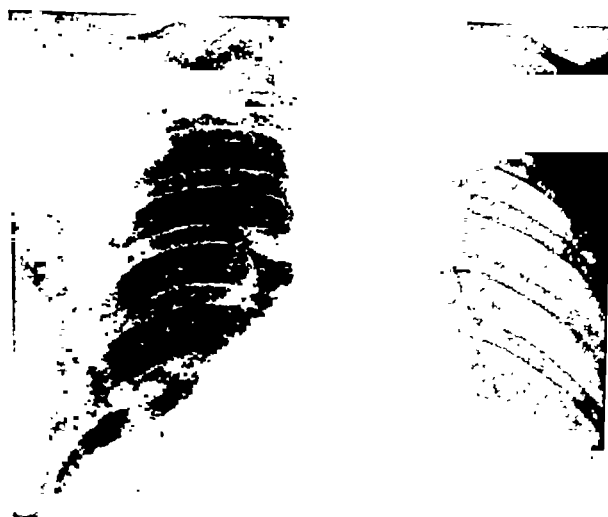


Fig. 53a.—Same as Fig. 53, showing the major resolution of the exudative response but with the permanent residual productive scarring.

Rather is there stimulated a slow, proliferative response, without any marked surrounding exudative reaction or lung involvement. The whole affair is very chronic and relatively benign.

This type of pulmonary tuberculosis, which we have termed the chronic productive form, usually starts at an apex and during the course of many years, slowly creeps downward toward the base of the lung. Because of the small dosage and the relative lack of exudative response, the individual lesions are small and discrete and surrounded by relatively normal lung. Occasionally, these individual lesions may coalesce to form larger areas of cirrhosis. At times, caseation may occur in the central portion of these areas and slough out to form a small cavity. When this happens, we are now dealing to all intents and purposes, with a caseous pneumonic form, although its mode of production may be quite different from the acute caseous lesion.

The symptom picture of the patient with the chronic productive form is sometimes very indefinite but at other times very striking. On our hospital services we usually see a patient in the fourth or fifth decade of life, who is admitted complaining of hoarseness or gastro-intestinal disturbance or some other extrapulmonary symptom. Generally, no mention at all is made of any respiratory disorder. It is only when the patient is closely questioned that he recalls a slight cough which he has always had as long as he can remember and a slight morning expectoration, which is usually blamed on smoking. There is generally admitted, too, some shortness of breath on exertion. The chronicity of the disease and the absence of acute allergic manifestations make it easy to understand this situation. Occasionally, however, especially in younger individuals, there may be slight low grade flare ups, with an increase in cough and expectoration, perhaps slight blood streaking and slight rises in temperature. These spikings, in an otherwise relatively smooth course, are probably due to small exudative foci resulting from slightly larger bronchogenic

spills. The patient quickly recovers his previous good health, however, and may continue for an indefinite period before experiencing another similar episode.

The ordinary uncomplicated chronic productive patient raises very little sputum. Tubercle bacilli are hard to find, even on concentration. Usually one positive sputum will be encountered in every ten to twenty specimens. Gastric examinations may sometimes yield the organisms when search of the sputum fails. It is this scarcity of organisms which serves to explain the benign character and the slow spread of this form of pulmonary tuberculosis.

If cavity formation occurs, then expectoration is increased and all the dangers and possibilities incident to the caseous pneumonic type of disease must be watched for. As a terminal affair in many of the advanced chronic productive cases, there seems to be a sudden change in the type of tissue reaction, so that each productive focus becomes an acute caseous focus. The patient becomes acutely ill and from this point on goes rapidly downhill, with cough and copious expectoration that is loaded with bacilli, as is seen in the caseous pneumonic form.

The physical signs in the patient with chronic productive tuberculosis are notoriously scant. The compensatory emphysema which surrounds the small, individual productive nodules readily masks whatever abnormal signs might be produced. Thus, very extensive pathology may be present without yielding any trace of its presence by means of physical signs. Generally, some slight alteration of breath sounds may be detected or a few fine râles heard, especially in the apices. It is the x-ray, however, which gives us the best evidence of the chronic productive form of tuberculosis. In the early stages, the lesion is confined to one or both apices. The shadowing instead of being diffuse and homogeneous, as in the exudative forms, is discrete and nodular, with relatively normal intervening lung. Occasionally, there may be small, acute exudative reactions corresponding with the clinical flare-ups. When these subside, the original productive lesion remains un-



changed. As the years advance and the disease progresses, the nodular shadows gradually creep downward toward the lower lung fields. When the lesion is extensive, almost the entire lung may be studded with these discrete nodules—so much so, in fact, that this type of *x*-ray has sometimes been diagnosed as chronic miliary tuberculosis. Closer inspection, however, will show the apicocaudal extension, with the greatest concentration of nodules in the upper poles of the lungs.

The treatment of the chronic productive form should resolve itself into the treatment of the occasional acute little flare-ups by bed rest and symptomatic treatment, and general supervision of the patient in the interim. The pathology in these patients may or may not slowly progress, in spite of rest and sanatorium care. It is, therefore, almost criminal to confine these patients to an institution for years, merely because serial *x*-rays show increases in pathology, the patient otherwise being perfectly well.

However, one must be exceedingly cautious lest there be overlooked a small cavity at an apex, from which a more rapid bronchogenic seeding of organisms can take place. If such a cavity be discovered, then the remarks concerning the caseous pneumonic form holds true and the patient is treated accordingly. Toward the latter phases of the illness, various complications may arise and must be treated as they present themselves. Not infrequently, a tuberculous meningitis is the terminal complication.

D. F. was first seen four years ago, because of a slight cold of three weeks' duration. There were no abnormal physical findings, the patient looked well; temperature and pulse were normal. She was seen in consultation only because of the *x*-ray picture, which was taken routinely by her employer, because of the cold. Figure 54 shows the appearance of the film at this time. It was felt at that time, that this girl did not have any activity of her tuberculosis. She was accordingly permitted to continue with her work. This patient remained perfectly well till a year and a half later, when she gave a history of having spat up some blood four weeks previously. Two weeks later, pain in the left chest appeared, the temperature became elevated and the patient took to her bed. The pain gradually subsided, but for one week prior to her examination, presented the typical findings of a pleurisy with effusion on the left side, with dulness and diminished to absent breath sounds. The temperature was 99.2° F.

It was felt that this girl had developed an acute pleural effusion, probably the result of a rupture of a small subpleural tubercle, with a discharge of its contents into the allergic pleura. A period of curing was recommended. The patient spent four months following a sanatorium routine, after which she returned to work and has been employed steadily since then. She has felt perfectly well and has had no pulmonary symptoms. Her x-ray series following the absorption of the effusion has remained stationary, except for a recent film, which suggests a slight increase in the shadowing and the possibility of cavitation at the left apex. Sputum examinations were negative for tubercle

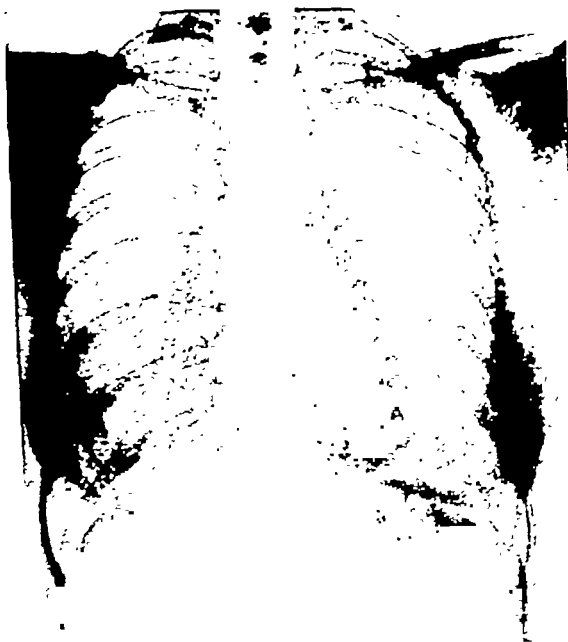


Fig. 54.—x-Ray of a twenty-year-old girl, showing the nodular type of shadowing at the apices, especially on the left, typical of the chronic productive tuberculosis.

bacilli. Gastric examination, however, showed the presence of organisms. This patient has been admitted to a sanatorium where pneumothorax treatments will be attempted on the left side in an effort to close the small apical cavity and thus prevent future bronchogenic spread.

This case illustrates the chronic productive type of tuberculosis, in a minimal stage and shows how it may spread insidiously without any noticeable symptoms. It also shows the importance of examining the gastric contents for tubercle bacilli when sputum is not obtained.

**To Recapitulate.**—For a clearer understanding of the natural history of pulmonary tuberculosis and subsequently a more intelligent application of therapeutic efforts, it is essential that the clinician be well acquainted with the various forms in which the disease may present itself. Depending upon the balance between allergy and dosage, and especially the latter, will depend whether the clinical form of the disease is either exudative or productive. The exudative forms may be one of three different types. There is a rapidly resolving form—the benign exudative. Here there is rapid resolution. The only treatment required is rest and protection from further contact with tubercle bacilli.

The exudative productive also clears by resolution, but not as rapidly or as completely as the benign exudative. Here again, recovery takes place without active intervention. The caseous pneumonic form, on the other hand, ends in slough and cavity formation from which there is a constant shedding of tubercle bacilli, to seriously threaten the remaining parts of the lung. It is this bad mechanical end-result of the caseous pneumonic form which must be energetically treated by the various forms of collapse therapy.

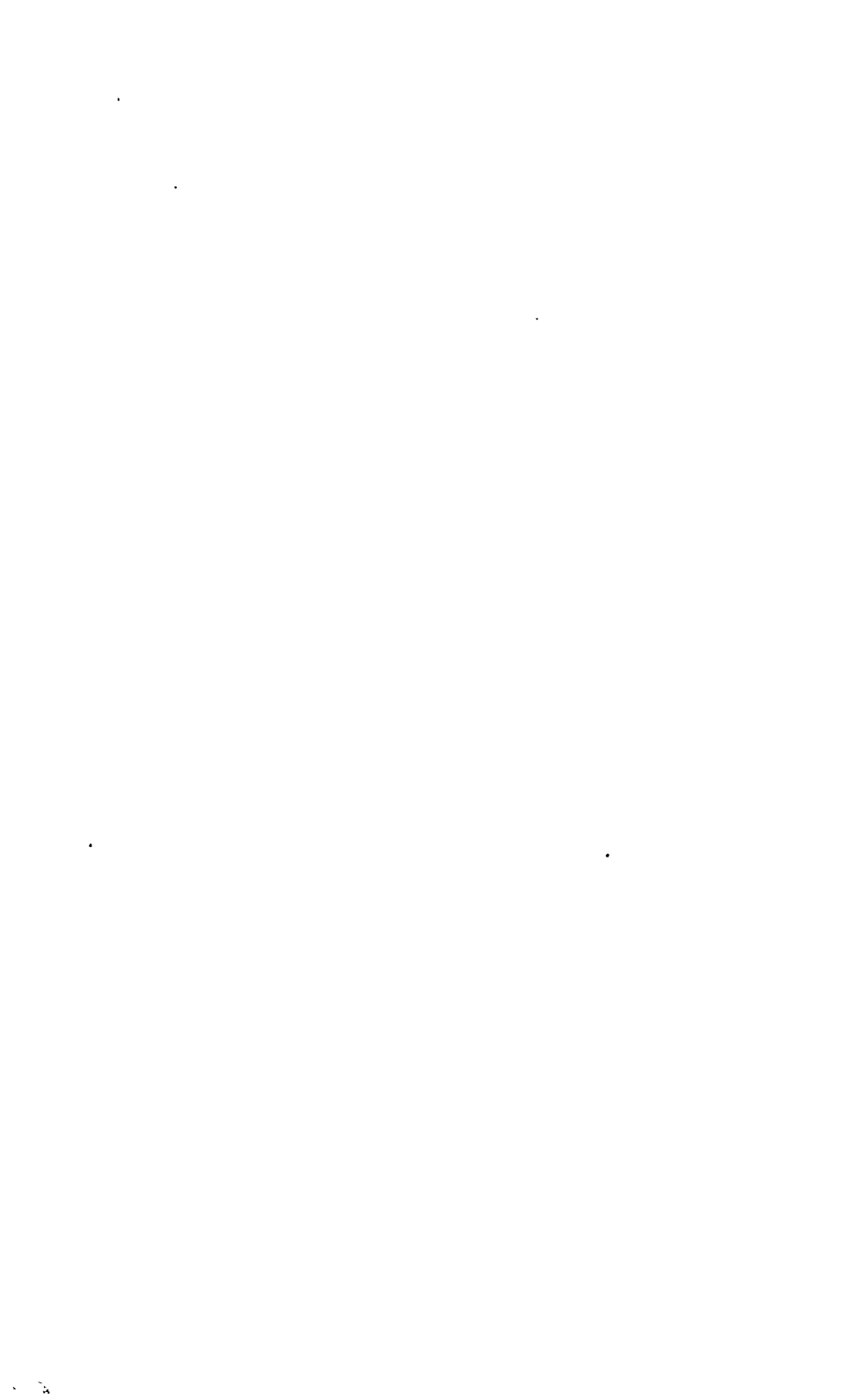
The chronic productive form is much slower in its onset and progress. Over the course of many years, it browses down from apex to base, the patient meanwhile for the most part feeling quite well. Treatment seems to have little effect unless definite cavity is present.

It should be remembered that there may be various combinations of these different forms of tuberculosis in the same individual. Thus, a person with a caseous pneumonic focus at an apex may have a resolving exudative spill into the contralateral lung. Regardless, however, of where the lesion occurs, or in what combination, or whether brought by the bronchogenic or hematogenous route, the principles involved are the same. Massive dosage produces one of the three forms of the exudative reaction. Small dosage causes a productive response. Our judgment must be based not on the quantity

of the disease but on a qualitative analysis. By keeping these few principles clearly in mind, we can more rationally evaluate the case and more logically apply our therapy.

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## CLINIC OF DR. DAVID REISNER

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#### HEMATOGENOUS TUBERCULOSIS OF THE LUNGS

HEMATOGENOUS tuberculosis of the lungs is frequently thought of as an acute, usually fatal disease and as a part of generalized tuberculous process which is characterized by diffuse and massive dissemination of miliary tubercles throughout the organs. While it is true that this condition is a well established entity, it must be looked upon as representing only an extreme event, that is, a severe generalized infection evidently caused by a sudden and massive invasion of tubercle bacilli into the blood stream. Because of the acute clinical picture and the characteristic pathologic changes, acute miliary tuberculosis has always been regarded as the classical manifestation of a hematogenous tuberculous infection. The various types of chronic generalized forms of tuberculosis and their corresponding pulmonary lesions have not received sufficient attention until recent years. It is now well recognized, however, that hematogenous tuberculous lesions may appear under a multitude of forms and phases with numerous gradations in extent and severity, ranging from very mild, abortive forms, through various intermediary types, to severe and fatal generalizations, as exemplified by acute miliary tuberculosis.

The various forms of hematogenous pulmonary tuberculosis represent in a large proportion of cases a part of a more generalized process. This will be discussed in greater detail later on. The pulmonary lesion, however, lends itself more easily to clinical investigation than the corresponding changes in other organs, as the changes in the lungs are readily demonstrable on radiographic examination. The recognition of the

hematogenous forms of pulmonary tuberculosis, especially of the chronic types, offers therefore an important index in the evaluation of chronic and protracted forms of systemic tuberculous infections.

A classification of hematogenous tuberculosis of the lungs into distinct types is extremely difficult because of a variety of intermediary phases and gradual transitions from one form into another. It would seem helpful, however, for the sake of clarity to postulate the following groups:

I. Diffusely disseminated hematogenous miliary tuberculosis, which may be subdivided into:

(a) Acute forms.

(b) Subacute and chronic forms.

II. Hematogenous forms of chronic pulmonary tuberculosis of varying extent, miliary or nonmiliary in type. This group may be subdivided into:

(a) Uncomplicated chronic hematogenous forms.

(b) Hematogenous forms with complicating bronchogenic progression.

#### I. DIFFUSELY DISSEMINATED HEMATOGENOUS MILIARY TUBERCULOSIS

As to the acute miliary tuberculosis, a detailed description of its well known clinical features and the corresponding pathological changes must be omitted here. The clinical manifestations may vary according to the preponderance of one or the other group of symptoms, this giving rise to the old established division into the pulmonary, the meningeal and the typhoid form. The average duration of illness from the onset until the fatal termination is generally between two and four, sometimes six weeks. It is important to mention, however, that it is difficult to set down definite time limits, a point which serves to emphasize how arbitrary a separation between acute, subacute and chronic forms of miliary tuberculosis may be. On one hand, there are cases showing a peracute markedly septic course in which the fatal termination may take place even within a few days in some extreme instances. Such cases

have been described under the term "sepsis tuberculosa acutissima," the clinical picture resembling an unusually severe general septicemia. Pathologically, such cases also differ from the usual miliary tuberculosis, inasmuch as no typical tubercles are found in the organs. Microscopically, however, there are found numerous small areas of necrosis which contain abundant acid-fast bacilli. There are, on the other hand, cases of miliary dissemination in the lungs which show a subacute or decidedly chronic course. Among the latter several types may be distinguished.

In some instances the onset may be acute with high fever and pronounced toxic symptoms. The course, however, is not progressive, the acute symptoms subside and the temperature becomes subfebrile or normal. Serial roentgen examination shows that the miliary dissemination throughout the lungs remains unchanged over a period of weeks or months. Eventually, after a prolonged illness, signs and symptoms of meningeal involvement may set in which results in fatal termination.

In other cases one misses entirely an acute phase of the disease, constitutional signs and symptoms are quite inconspicuous. Physical signs over the lungs may or may not be found. In such cases one is usually greatly astonished to find the typical miliary dissemination in the lungs on roentgenographic examination and the diagnosis of miliary tuberculosis is at times viewed with skepticism because of the marked contrast between the roentgen findings and the general clinical aspect of the case. In a number of cases the miliary dissemination in the lungs is preceded by pleural effusion, sometimes recurrent, which may be either uni- or bilateral. This also applies to cases of acute and fatal forms of miliary tuberculosis.

The further course and evolution of the disease in cases of chronic or latent miliary tuberculosis of the lungs does not behave uniformly. Some patients remain asymptomatic and apparently well for an indefinite period. The objective findings in the lungs may show no further change. However, as in the subacute forms, a complicating meningitis is not infre-



quently the eventual cause of death. In other cases metastatic lesions of a localized nature may develop in the peripheral organs, such as in the bones or joints, urogenital tract, serous membranes, sometimes skin or eye manifestations may appear. In such cases it is often difficult to establish, however, whether these lesions were preexistent or whether they followed the pulmonary dissemination. In the absence of such complications these individuals may remain perfectly well and symptom-free, although the pulmonary changes are persistent.

In some cases showing a clinically favorable course, progressive resolution of the pulmonary changes may be observed on serial roentgen ray studies. The process of resolution is usually slow, extending, as it does, over a number of months, or years. The end-result may be either complete or incomplete clearing. The former is more apt to take place in cases showing dissemination of soft foci which often appear larger than miliary size. In other cases there remain residual changes, such as sparsely scattered discrete nodules, with or without calcification, or a more or less diffuse increase in the linear markings due to interstitial fibrosis.

Although doubted for a long time, there are now sufficient observations available to indicate that healing of a hematogenous pulmonary dissemination is a distinct possibility, not only in the clinical but also in an anatomical sense. From an anatomical standpoint complete disappearance of the focal dissemination is quite conceivable, since in a number of instances the hematogenous spread may result in the formation of disseminated small exudative pneumonic foci, miliary alveolitis, and very little proliferative tissue reaction. Such changes are capable of partial or complete resolution. In other instances the healing process consists in transformation of the miliary tubercles into hyaline connective tissue nodules with resulting cicatricial shrinkage. These changes in conjunction with the subsequently developing emphysema account for the fact that such slight residual foci may entirely escape visualization on the roentgenogram. Healing with calcification con-

stitutes, of course, a persistent anatomical change and is easily demonstrable radiographically. In some cases the process of healing may result in the production of interstitial fibrosis

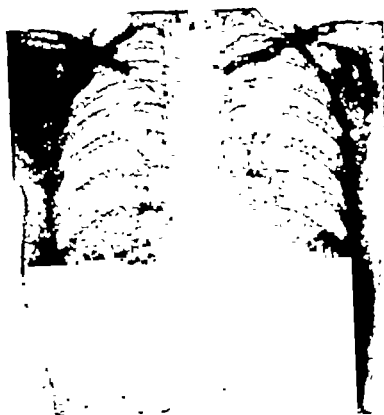


Fig. 54a.—Diffusely disseminated, healed, calcified, miliary tuberculosis. No clinical symptoms; accidental finding. (Courtesy of Dr. George Cole.)



Fig. 54b.—Roentgenograms of a patient with tuberculosis of kidney and multiple lymphoglandular involvement. A, shows disseminated hematogenous tuberculosis in both lungs. Seven months later (B) there was almost complete resolution of the changes.

along the peribronchial and perivascular lymphatics, "lymphangitis reticularis." This may find its expression on the roentgenogram in the form of fine linear strands causing accentuation of the pulmonary markings.

As regards the pathogenesis of miliary tuberculosis, there has been a tendency to view the development of hematogenous spreads as mere accidental occurrences caused by a sudden invasion of bacilli into the blood stream. Gross anatomical alterations, such as perforation of a caseous pulmonary focus into a blood vessel, or ulceration of a caseous tubercle situated in the intima of a vein, or in the wall of the thoracic duct, are considered as the principal sources of hematogenous disseminations. The bacilli may then be distributed either through the pulmonary circuit, through a part or the whole of the general circulation, or both.

There is little doubt that such events may be responsible for the development of acute and massive generalized forms of miliary tuberculosis. But it must also be borne in mind that tubercle bacilli may enter the blood stream by an indirect route without gross mechanical alterations of anatomic structures. There may be a continuous or intermittent discharge of smaller or larger doses of bacilli into the circulation from a variety of sources. The changes resulting from the primary complex probably provide a frequent source of hematogenous involvement. This may originate either in the primary pulmonary focus, but probably more often in the regional tracheobronchial lymph nodes. The bacilli may extend into the circulation by way of the lymphatics into the thoracic duct, from these into the large veins, and the right heart. There are, of course, other potential sources of blood stream dissemination, such as, postprimary pulmonary foci, or various latent or manifest caseous extrapulmonary foci. That the anatomical changes resulting from the primary infection serve as an important source of hematogenous dissemination, is indicated by the fact that generalized forms of tuberculosis are considerably more frequent during infancy and early childhood than in later life, the so-called "early generalization." This is probably accounted for by the fact that in its active stage the primary complex harbors tubercle bacilli of sufficient number and virulence to give rise to extensive dissemination of the disease. As the primary lesion undergoes progressive healing such inva-

sions become both less frequent and probably less severe, as far as the resulting spread is concerned.

It is readily seen that there are manifold possibilities and circumstances leading to hematogenous dissemination and the resulting spread will, therefore, vary greatly in its distribution, extent and severity. There can be no doubt, of course, that the dosage of bacilli and their virulence, as well as the anatomical distribution, are of foremost importance and that variations of these factors may to a great extent account for the variable clinical picture and evolution of the disease, as outlined before. In addition to these, however, there are probably other factors, about which we have as yet little exact knowledge, that may either enhance or retard the development of a hematogenous disease process. Variable conditions of specific allergy and resistance or relative immunity, may greatly modify the consequences of invasion of bacilli into the circulation. It is very probable that the mere presence of tubercle bacilli in the blood stream does not necessarily have to cause generalization of the disease. This is indicated by the observation that in the progressive and destructive forms of pulmonary tuberculosis, although there are ample opportunities for invasion of the bacilli into the circulation, acute generalized miliary tuberculosis and meningitis, as well as manifest extrapulmonary hematogenous metastases of chronic nature, represent a relatively infrequent occurrence. This would seem to suggest a certain antagonistic relation between local progression and generalization of the tuberculous process which may be closely related to specific allergy and the state of relative immunity. There are, on the other hand, certain factors of nonspecific nature which by lowering the state of general resistance may serve as predisposing causes for the actual outbreak of generalized tuberculosis. Among these should be mentioned chronic debilitating diseases, such as cancer or the leukemias; intercurrent acute nontuberculous infections; postoperative conditions, puerperium, old age, and others. Such observations offer grounds for the assumption of a latent or chronic protracted tuberculous bacteremia, al-

though it must be admitted that direct bacteriological proof is difficult to establish with our present methods. An overwhelming massive infection will, of course, under any and all circumstances, lead to an acute and fatal spread. However, given a more limited invasion and favorable general conditions, the resulting pathological changes and corresponding clinical manifestations may show great variations, from subacute or chronic types to very mild or latent forms of hematogenous dissemination.

It is essential to point out that the pulmonary dissemination found in the chronic forms of miliary tuberculosis represents in most instances only a part of a generalized process, just as in the typical acute forms, but in a much milder form. In such cases postmortem examination usually reveals evidence of some spread through the organs of the general circulation, such as, scattered tubercles in the liver, spleen, kidneys, adrenals, etc. These changes are often quite inconspicuous in comparison with the pulmonary findings. The anatomic peculiarities of the pulmonary circulation and the fact that the lung acts as a sort of filter for circulating bacilli, probably account for the predominance of the hematogenous dissemination in the lungs. Whatever the source of bacillary invasion, generally speaking, the lungs bear the brunt of the hematogenous distribution to a much greater extent than any other single organ. In some instances, however, the miliary dissemination may be limited to one or more parenchymatous organs outside of the lung and involve the latter to a much lesser extent or not at all. This may be the consequence of invasion of bacilli into a part of the arterial circuit. On rare occasions such limited disseminations in the organs undergo calcification, similarly as in the lungs, and may be demonstrated on the roentgenograms.

Clinical observation and analysis of postmortem findings in cases of chronic protracted forms of hematogenous tuberculosis, suggest that the changes in various organs may occur at successive intervals and that they may be due to repeated

invasions of bacilli into the circulation. The above-mentioned pleural effusions preceding the pulmonary dissemination or the fact that a number of cases of chronic, apparently benign miliary dissemination in the lungs finally develop a complicating fatal meningitis, may well be explained on that basis. It, therefore, seems that the total course of many cases of sub-acute or chronic miliary tuberculosis of the lungs represents a series of successive phases which under unfavorable circumstances may eventually lead to generalization of the disease and fatal termination. On the other hand, in the absence of a progressive spread and grave complications, such as particularly meningitis, clinical recovery is well within the realm of possibility. It is the ever-present danger of a potential generalization which renders the ultimate prognosis of chronic and latent forms of miliary tuberculosis of the lungs so uncertain.

## II. HEMATOGENOUS FORMS OF CHRONIC PULMONARY TUBERCULOSIS

The hematogenous forms of chronic pulmonary tuberculosis to be discussed below must be distinguished, on one hand from the typical miliary dissemination, and on the other hand from the common types of lesions which constitute the vast majority of cases of chronic pulmonary tuberculosis. It may be said that these forms occupy an intermediary position between the classical miliary forms and the ordinary chronic phthisis.

Chronic hematogenous pulmonary tuberculosis presents a large variety of types and stages which differ greatly both as to the extent and the morphological characteristics of the changes. The foci are either of the miliary or of the conglomerate acino-nodose type. Still greater are the variations in the extent of the pulmonary changes ranging from few scattered, sometimes calcified nodules in the apices to a diffusely disseminated spread throughout the lungs. There are various intermediary forms, such as involvement of the upper one third, or of the upper halves, or else of the upper two thirds of both lungs. The features which are constantly

present and which may be considered as characteristic for chronic hematogenous forms are as follows: the disseminated



Fig. 54c.—Hematogenous form of chronic pulmonary tuberculosis associated with bilateral pleurisy. The roentgenogram shows bilateral symmetrical discrete nodular dissemination, predominantly localized in the apices and subapical areas; bilateral pleural effusion, more marked on the left side.



Fig. 54d.—Chronic hematogenous tuberculosis of the lungs. Roentgenogram shows bilateral symmetrical nodular dissemination through the upper portions of both lungs; marked emphysema of the basal portions. Clinical symptoms very slight; sputum negative for tubercle bacilli.

character of the lesion; the bilateral symmetrical distribution; the continuous apicocaudate spread, the foci usually decreas-

ing in size and in number from apex to base; finally, the discrete nodular character of the foci which are of the predominantly productive type. Recurrent unilateral or bilateral pleural effusions are not infrequently associated with these types of chronic pulmonary tuberculosis and must be regarded as a manifestation of hematogenous involvement (Figs. 54c and 54d).

Roentgen examination is of paramount importance in the detection of these lesions. Clinically, in a large proportion of the cases the existence of pulmonary changes is not suspected. They are occasionally discovered on routine roentgenographic examination. This is due to the fact that clinical signs and symptoms are often either entirely absent or extremely slight. Physical examination of the lungs frequently reveals very few abnormal findings, sometimes signs of emphysema or bronchitis. The disproportion between the paucity of clinical signs and symptoms referable to the lungs on the one hand, and the objective changes as revealed on the roentgenogram, on the other, is a striking feature of the chronic hematogenous pulmonary tuberculosis. As a rule, no tubercle bacilli are found in the sputum, in some instances a small number of bacilli may be present occasionally in a large series of concentrated specimens.

An impressive feature of typical hematogenous forms of chronic pulmonary tuberculosis is the absence of gross areas of infiltration, of ulceration and excavation. This is in distinct contrast to the common bronchogenic forms of chronic pulmonary phthisis which are characterized by the presence of these very changes. However, a strict differentiation between chronic hematogenous and bronchogenic forms may often be quite difficult since in a considerable proportion of cases of originally hematogenous lesions, the characteristic features become greatly altered as a result of superimposed bronchogenic involvement. A gradual breaking in of interstitial foci into the air passages evidently accounts for the development of such combined forms. This occurrence naturally opens the way for further bronchogenic progression with ul-



ceration and cavity formation. Clinically this complication manifests itself by the appearance of signs and symptoms of activity and positive sputum. Radiographically there will be found larger coalescent infiltrative foci, in addition to the discrete nodular dissemination, as well as cavity formation. The presence of the latter is at times difficult to determine from the roentgenogram because of their small size, the diffuse pulmonary changes and the frequently present emphysema.

Occasionally the cavities found in connection with chronic hematogenous lesions are of a peculiar appearance, thin-walled, either single or multiple. These cavities are often referred to as the "punched-out" variety and it is assumed by some that they represent a part of a hematogenous process. It should be mentioned, however, that the pathogenesis and the mechanism of development of these cavities has not been sufficiently clarified as yet.

In many cases one may find evidence of superimposed bronchogenic progression in the upper pulmonic fields, while the more dependent portions retain the discrete nodular dissemination. This, in conjunction with the symmetrical distribution of the lesion indicates the hematogenous character of the original process. In other instances, however, the changes resulting from the secondary bronchogenic spread may become the predominant feature of the lesion to such an extent that it is extremely difficult, if not impossible, to determine its original character, unless one has had an opportunity to follow the evolution of the process by means of serial roentgenograms. Occasionally the complicating bronchogenic involvement may cause little progressive and destructive changes showing instead a marked tendency to fibrous tissue formation. The eventual picture found in such instances is a bilateral, symmetrical, cirrhotic-indurative process involving predominantly the upper lobes, often associated with numerous small bronchiectases and marked compensatory emphysema of the lower portions of the lungs. Clinically these cases frequently show a stationary course over a period of many years, in spite of persistently positive sputum.

The pathogenesis of this group of chronic hematogenous pulmonary tuberculosis is essentially governed by similar principles as those outlined in connection with the various forms of miliary disseminations. The differences between these two groups concern largely the extent of the lesion, its morphological character and the course. Because of the more limited extent of the pulmonary lesion, its exceedingly chronic duration and the added secondary changes, there may often be only a distant resemblance between the chronic hematogenous forms and the typical miliary dissemination, as far as the character of the pulmonary findings is concerned. The significant point, however, is the fact that the hematogenous group of chronic pulmonary tuberculosis represents to a large extent a part of a chronic generalized process. In a considerable proportion of cases these types of chronic pulmonary lesions are found in association with various forms of extrapulmonary metastatic manifestations, such as, tuberculosis of bones and joints, of the urogenital tract, the serous membranes, generalized lymphoglandular involvement and others. The frequent coexistence of extrapulmonary hematogenous involvement and pulmonary lesions of the type here described is an important indication of their hematogenous origin. A recent study revealed that about two-thirds of the pulmonary lesions found in association with extrapulmonary involvement, presented characteristic features of the hematogenous group. It must be borne in mind, however, that chronic pulmonary lesions of an identical character are often enough found in cases which present no evidence of manifest metastatic foci elsewhere. Conversely, there may be extensive extrapulmonary tuberculosis without any evidence of pulmonary changes other than the old primary complex. These differences in the localization of the hematogenous spread are probably determined by a number of factors. The anatomic position of the source of bacillary discharge, as discussed in a preceding paragraph, variable organ susceptibility, as well as mere chance location may all be responsible to a greater or lesser extent.

It will be found, however, that although the predominant

lesion may be limited to one or several organs, there is usually also evidence of some distant dissemination. In many cases of chronic and progressive extrapulmonary tuberculosis the pulmonary changes are merely in the nature of an incidental finding, such as sparsely disseminated nodules. Similarly post-mortem examination reveals that almost all cases of hematogenous involvement of the lungs, although showing no clinical evidence of extrapulmonary lesion, present some dissemination in other organs which is often purely abortive in character. From a clinical standpoint such cases may be regarded as chronic isolated hematogenous tuberculosis of the lungs.

The ultimate fate and hence the prognosis of chronic hematogenous forms of pulmonary tuberculosis is largely determined by their inherent tendency to progressive hematogenous propagation of the disease, a point already emphasized in connection with the atypical forms of miliary tuberculosis. Though the pulmonary lesion may appear quite harmless one must always keep in mind the possibility of some unpredictable developments, such as, various metastatic lesions of chronic nature, especially skeletal and genito-urinary involvement, meningitis and acute generalized miliary dissemination.

The differential diagnosis of acute and chronic forms of hematogenous pulmonary tuberculosis should, of course, consider a variety of other pulmonary lesions of a disseminated character, such as diffuse carcinomatosis, pneumoconiosis, diffuse bronchiolitis, chronic vascular stasis, disseminated non-tuberculous miliary bronchopneumonia and disseminated bronchogenic tuberculous spreads. The diagnostic features of these lesions cannot be discussed here in detail. A few words must be said, however, regarding the diffuse focal bronchogenic tuberculous dissemination, which usually occurs following hemoptysis. The differentiation from hematogenous dissemination rests on the history of a preceding recent hemoptysis. The presence of an infiltrative and usually excavating lesion in the lung, the lack of uniform distribution of the changes and the variable size of the foci, are points in favor of a posthemoptysis spread. A consideration of the general

clinical aspects and of the physical findings in the chest, which are as a rule more pronounced in cases of posthemoptysis spread, will also aid in the differentiation between hematogenous and bronchogenic dissemination.

As regards the treatment of the various types of chronic hematogenous pulmonary lesions, it must be pointed out that in a considerable proportion of such cases it is the extrapulmonary process which demands the sole therapeutic attention, as the pulmonary changes frequently represent only an incidental finding. Many cases in which the hematogenous lesion appears confined to the lungs and is limited in extent require no particular treatment and are not in need of institutional care. Such cases may lead a perfectly normal life over a period of many years. Of course, periodic examinations are essential, because of the possibility of activation and progression of the pulmonary lesion and in view of a potential extrapulmonary spread. Other cases, showing more extensive spreads, require prolonged rest treatment with a proper hygienic, dietetic régime. Cases in which the original hematogenous lesion is complicated by superimposed bronchogenic progression and cavitation require active treatment. Collapse therapy is quite difficult in such cases as the disease is invariably bilateral. If the process is not too extensive, the application of bilateral artificial pneumothorax should be seriously considered. However, the marked chronicity of the pulmonary lesion and the frequent pleural involvement resulting in obliteration of the pleural spaces, very often preclude a successful pneumothorax treatment.

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## CLINIC OF DR. GEORGE G. ORNSTEIN

### SEA VIEW AND METROPOLITAN HOSPITALS

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#### MANAGEMENT OF FAR ADVANCED TUBERCULOSIS

PNEUMOTHORAX is not only universally accepted, but has become the principal mainstay in the treatment of pulmonary tuberculosis. Whereas, a decade ago, the treatment was reserved as an emergency measure, today, pneumothorax is urged as soon as a diagnosis of cavity is made. There is still a large number of physicians who believe that all patients should be given a period of rest with the hope of spontaneous resolution of the tuberculous disease. We have found that in the caseous pneumonic forms of tuberculosis, spontaneous resolution with disappearance of tubercle bacilli occurs only in a small percentage of cases (15 to 20 per cent), and that there is a greater possibility of progression of the disease. In discussing the caseous pneumonic tuberculosis we refer to that malignant form of the disease described by Ornstein, Ulmar and Dittler.<sup>1</sup> In brief, "caseous pneumonic tuberculosis" is the open cavity case; the cavity is usually demonstrable in the x-ray, and tubercle bacilli are easily identified on examination of the sputum. In the past, little attention was paid to x-ray and positive sputum, provided the patient was free of toxic symptoms and had added considerable weight. We have learned by bitter experience that fat patients with positive sputum who are considered "temporarily safe," usually die in a few years because of a spread of the disease.

Pneumothorax, therefore, is now indicated whenever a diagnosis of cavity is made. This treatment is used chiefly in unilateral cases of tuberculosis, and is also used in bilateral

cases where the preponderance of the disease involves one lung. In the above types, the results have been both satisfactory and sufficiently gratifying to influence every sanatorium throughout the country to adopt the use of pneumothorax in pulmonary tuberculosis.

It was but a natural step for a group of more intrepid workers to gaze upon the advanced bilateral forms of pulmonary tuberculosis and believe that pneumothorax might be applied with some hope of success.



Fig. 55.—An x-ray of a patient with bilateral pneumothorax. The cavities in both upper lobes are prevented from closing by multiple adhesions. Sputum positive for tubercle bacilli.

At the Metropolitan and Sea View Hospitals, a small number of cases was selected for bilateral pneumothorax. The chief difficulty to face in bilateral pneumothorax was the problem of sufficient lung ventilation. It was also found that in the advanced case, more adhesions were usually present than in the unilateral case. Because of the adhesions, the normal uninvolved lobes were collapsed with the diseased portions of the lung. The patients became dyspneic, and because of the anoxemia, were depressed and irritable. Peculiarly, even with complete rest in bed, where there is anoxemia there is a pro-

gressive loss of weight. In cases with no complicating adhesions, selective collapse of the diseased areas was obtained with no symptoms of anoxemia.

We realized that if the adhesions could be severed, we might obtain the desired selective collapse of the diseased lung and the compressed atelectatic normal lung tissue could be re-



Fig 56.—x-Ray of the same case as Fig. 55. A closed pneumonolysis was done on both sides. Note the complete closure of the cavities in both upper lobes. Sputum negative for tubercle bacilli.

expanded. However, we were fearful about the reaction of the patient to closed pneumonolysis with both lungs partially collapsed, but were pleasantly surprised to find how comfortably the operation was tolerated. After the diseased area was collapsed and the normal lung tissue reexpanded, a closed pneumonolysis was tried on the contralateral lung. Figure 55 is an example of an unsuccessful bilateral pneumothorax in



advanced pulmonary tuberculosis. Figure 56 is an x-ray of the same patient following a bilateral closed pneumonolysis.

With the help of the surgical service we now have a means of controlling the advanced bilateral pulmonary tuberculous disease. Closed pneumonolysis is not a simple procedure in the advanced disease. The adhesions must be severed if we are to have any hope of success. Whereas in the unilateral case the surgeon should take no risk with closed pneumonolysis, in the bilateral case he must have the courage to "go the limit" in severing difficult adhesions. In the unilateral case there is no reason for risking a spontaneous pneumothorax and complicating empyema, because a thoracoplasty could easily control the tuberculosis should pneumothorax fail.

Difficult adhesions have been successfully cut by a combination of blunt dissection and cautery. And in our institutions under the stimulating influence of Dr. Pol N. Coryllos, the surgical staff has become very adept in the handling of these wide and difficult adhesions. In some cases as many as seven adhesions are severed at one time, while in other cases as many as four different attempts at closed pneumonolysis have had to be made before the adhesions have been successfully cut. It is safer to do a little at a time and try again, than do too much in a difficult case. As our experience increased, we decided that by following a definite pattern we might be more successful and produce less anoxemia, than by a "hit-and-miss" method.

The anoxemia could be avoided by obtaining a selective collapse of the diseased portion of the lung without sacrificing normal lung tissue. We decided to do one lung at a time, which would prevent a marked decrease in vital capacity. Our experience was not favorable to simultaneous collapse of both lungs. There was both more chance of anoxemia and less chance for successful closure of cavities. The pattern, therefore, was to start with the more involved side. If adhesions were present, within two or three weeks, or as soon as there was enough space to introduce the thoracoscope, a closed pneumonolysis was to be attempted. The adhesions were to

be severed, the diseased areas of lung collapsed and the normal lung tissue reexpanded to its fullest extent. With the collapse of one lung the contralateral lung was to be collapsed in a similar manner.



Fig. 57.—x-Ray of an advanced bilateral pulmonary tuberculosis. Note the diffuse distribution of the tuberculosis and the multiple cavities in both lungs.

The following is a typical example of the method we have adopted in the treatment of advanced bilateral pulmonary tuberculosis:

A young white female, twenty-six years of age, had been on the wards of the Metropolitan Hospital for sixteen months. Her tuberculosis was so far advanced that the visiting staff had decided that there was very little hope for improvement even with the use of pneumothorax. They believed that if both lungs were collapsed there would be insufficient vital capacity to carry on. Her sputum was laden with tubercle bacilli. Figure 57 is an x-ray of the lungs of this patient taken on March 13, 1935. The case was presented to the surgical conference, and it was decided there to collapse the left lung first

If, after induction of pneumothorax, adhesions complicated the pneumothorax, they were to be cut by closed pneumonolysis. Whatever normal lung tissue was present was to be reexpanded at once, and a similar procedure followed on the contralateral side.

A primary pneumothorax on the left was started on March 25, 1935. We soon decided that the pneumothorax would not be successful because of adhesions to both the upper and lower lobes. On May 2, 1935, Dr. Coryllos did



Fig 58—See Fig 57. A pneumothorax was induced on the left. Because of multiple adhesions to the upper lobe an exploratory thoracoscopy was performed and all adhesions to the upper lobe severed. Note the selective collapse of the left upper lobe. Note the large cavity in the apex of the left lower lobe. Another exploratory thoracoscopy was done and a large adhesion severed with closure of the cavity in the apex of the left lower lobe.

an exploratory thoracoscopy, and successfully severed seven adhesions to the upper lobe. The left upper lobe collapsed, but because of a long adhesion to the apex of the lower lobe, a large cavity still remained open (Fig. 58). On June 17, 1935, Dr. Coryllos again did an exploratory thoracoscopy and was successful in severing the remaining adhesion. Pneumothorax was so managed that the diseased lung was collapsed and the normal uninvolved tissue allowed

to reexpand (Fig. 59). Because the disease involved both lobes of the left lung, the whole lung had to be first collapsed to close the cavities. When the cavities were closed, the normal lung tissue was allowed to reexpand. This occupied almost five months. We then decided to collapse the contralateral lung. On October 3, 1935, a pneumothorax was induced on the right side. Again, adhesions prevented a complete collapse of the right upper lobe. Figure 60 demonstrates the many adhesions preventing the collapse of the right upper lobe. On December 5, 1935, Dr. Coryllos did an exploratory thoracoscopy. Two adhesions were severed with a successful collapse of the right upper lobe. From

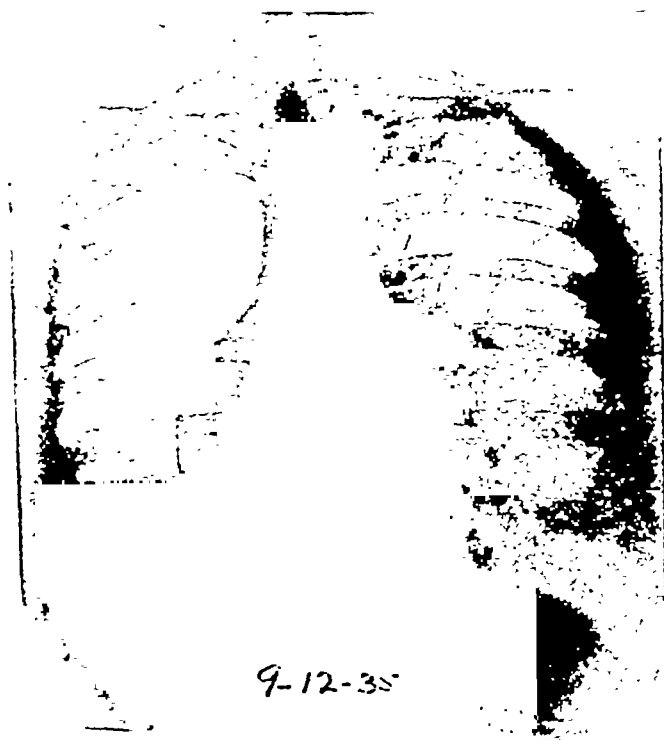


Fig. 59.—The left thorax is on the reader's left hand side. See Figs. 57, 58. Note the reexpansion of some of the uninvolved portion of the left lung.

then on, the patient's sputum was free of tubercle bacilli. Figure 61 is an x-ray taken before the patient was discharged to the out-patient department where she receives a weekly refill. Notice the complete collapse of the involved areas of both lungs and the good expansion of the healthy lung tissue. There is only a small amount of effusion on the left side. There was no evidence of anoxemia. Here, we have an example of what can be done with a hopelessly advanced case of tuberculosis involving both lungs—sputum rendered free of tubercle bacilli in less than nine months, and with a good chance of its remaining free of bacilli.

An analysis of our results at the Metropolitan Hospital prophesy a more hopeful future for the advanced case. In 48 cases there were 27, or 56 per cent, in which a negative sputum was obtained. Twenty-one, or 44 per cent, still have



Fig. 60.—See Figs. 57–59. The left lung is on the reader's left hand side. The disease in the left lung has been controlled. A pneumothorax is induced on the right side. Note the partial collapse of the right upper lobe. Multiple adhesions prevent the collapse of the right upper lobe. The sputum is still positive.

a positive sputum or have died. This group includes 15 deaths. An analysis of the deaths is as follows:

- 1—Empyema.
- 1—Miliary tuberculosis
- 1—Cardiac death.
- 1—Tuberculous meningitis
- 2—Severe hemoptysis.

- 2—Extensive intestinal tuberculosis.
- 2—Unsuccessful closed pneumonolysis—the adhesions could not be severed, and the disease spread.
- 5—Extensive bronchogenic spread of the disease.



Fig. 61—See Figs. 57–60. The left lung is on the reader's left hand side. Note the complete selective collapse of the right upper lobe after severing two adhesions by a closed internal pneumonolysis. All the diseased areas in both lungs are controlled. The sputum had been free of tubercle bacilli for over three months when this x-ray was taken. In nine months a hopelessly advanced case has been transformed into a case with a very hopeful future.

Twenty-six cases, or 54.1 per cent, of the 48 required either a unilateral or bilateral closed pneumonolysis.

Unilateral closed pneumonolysis cases, 17:

Negative sputum	11
Positive sputum	6

Bilateral closed pneumonolysis cases, 9:

Negative sputum	3
Positive sputum	6

Out of the positive sputum cases there were two in the unilateral pneumonolysis group and two in the bilateral pneumonolysis group with sputum positive only on concentration. Few bacilli were seen on examination of the concentrated sputum. The patients were clinically improved. It has been the custom at both the Metropolitan and Sea View Hospitals to accept only a negative sputum as evidence of control of the disease.

Spontaneous pneumothorax occurred in 8 patients. All recovered except one, listed as dying of an empyema. In one patient spontaneous pneumothorax happened on three different occasions with recovery. In another patient this unpleasant complication occurred twice with recovery.

When we compare the above results with the figures of Barnes and Barnes,<sup>2</sup> who reported over 80 per cent deaths within a year after admission to the sanatorium in cases with a less severe form of pulmonary tuberculosis, we must accept bilateral pneumothorax supplemented by closed pneumonolysis as a definite advance in the management of the far advanced case of bilateral pulmonary tuberculosis. The death rate in this group is only 31.2 per cent, compared with 80 per cent of Barnes and Barnes, and 56 per cent of our group have persistently negative sputum.

An analysis of the Sea View group is as follows:

	<i>Negative sputum.</i>	<i>Positive sputum.</i>	<i>Died.</i>	<i>Total.</i>
1933.....	2.0	2.0	0.0	4
1934.....	9.0	6.0	5.0	20
1935.....	12.0	11.0	13.0	36
1936 (Jan. to June)...	6.0	4.0	8.0	18
Total.....	29.0	23.0	26.0	78
Percentage.....	37.2	29.5	33.3	100

An analysis of the combined 126 cases:

	<i>Negative sputum.</i>	<i>Positive sputum.</i>	<i>Died.</i>	<i>Total.</i>
Total.....	56.00	29.00	41.00	126
Percentage.....	44.44	24.02	32.54	100

In the bilateral advanced pulmonary tuberculosis in which collapse therapy through pneumothorax is not possible because of an adherent pleura, there is still the possibility of employing other surgical procedures. We would refer the reader to a recent article by Coryllos and Ornstein<sup>3</sup> on the surgical management of bilateral cavernous pulmonary tuberculosis.

When one lung can be controlled by pneumothorax, a thoracoplasty may be attempted on the contralateral side. These authors in selected cases have used bilateral thoracoplasty for the control of bilateral tuberculosis.

### SUMMARY

An attempt has been made to present a method of control of the advanced case of bilateral pulmonary tuberculosis. The results obtained prophesy a more hopeful prognosis in the arrest of the disease in the advanced case of bilateral pulmonary tuberculosis.

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CLINIC OF DRS. ARTHUR J. GREENBERGER  
AND MONROE E. GREENBERGER

SEA VIEW HOSPITAL

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UROGENITAL TUBERCULOSIS ASSOCIATED WITH  
PULMONARY TUBERCULOSIS

IN our experience, both clinically and at autopsy, genito-urinary tuberculosis is associated with pulmonary involvement. This fact is readily understood when you consider that out of 1650 patients at Sea View Hospital 1400 have been hospitalized chiefly because of pulmonary involvement. Reports by Young and others reveal definite involvement of the lungs and pleura in only 28 to 40 per cent of the cases of urological tuberculosis.

RENAL TUBERCULOSIS

It is our opinion and it is generally conceded that the kidney is first invaded in tuberculosis of the urinary tract. Tubercle bacilli gain entrance by way of the blood stream. We have never noted a case of isolated renal tuberculosis. In a series of 500 postmortem examinations that we reported in June, 1934, 484 of the cases came to autopsy because of pulmonary tuberculosis and only 16 due to extrapulmonary tuberculosis.

In a general hospital about 30 per cent of all nephrectomies are performed because of an underlying tuberculosis. Wildbolz reports 55 per cent of his nephrectomized cases well after ten years, whereas 58 per cent treated medically died within five years. Persson showed that 85 per cent of the cases treated medically died within five years.

Medlar is of the opinion that the disease is always bilateral; in his animal experiments the lesion appeared bilaterally in

88 per cent. Folsom called attention to the fact that the renal tuberculosis produced experimentally by Medlar does not correspond to the chronic renal tuberculosis as seen by the clinician. Likewise the tuberculous areas found by him in the kidneys at autopsy are often manifestations of a terminal miliary tuberculosis. Of the 500 cases in our series in which necropsy was performed, 252 showed evidence of tuberculous infection. Miliary tubercles were found in 228, or 45.6 per cent. By this we mean small tubercles that can be recognized grossly. Microscopic examination of these sections revealed that they vary from necrotic areas to fibrotic tubercles. In this group we found the disease to be bilateral in 82 per cent. We called attention at that time, that in the terminal stage of pulmonary tuberculosis, hematogenous dissemination of tubercle bacilli is a frequent occurrence and gross and microscopic tubercles can be found in the liver, spleen and kidneys. These areas of tubercle formation found at the necropsy table are not to be regarded as evidence of a previously existing clinical tuberculosis, but as a phase of the terminal generalization from another organ tuberculosis, usually pulmonary. It is probable that this explains the unusually high percentage of miliary tuberculosis found in our series and reports of other investigators. Clinically, this type of renal infection is of little significance. It rarely is accompanied by urinary symptoms, has no evidence of pyelographic changes from the normal and is demonstrable only at postmortem examination. This type is commonly referred to clinically as the nondestructive, closed lesion. Organ tuberculosis is the pathologic condition most frequently encountered by the clinician. It is the type of lesion that shows definite pyelographic changes and is clinically recognizable. In our autopsy series only 4.8 per cent of the cases revealed destruction of the kidney substance. It is our thought that most of the arguments and differences of opinion between pathologist and urologist as to whether a case should be treated medically or surgically are based on the fact that the pathologist thinks in terms of the very common miliary

nondestructive lesion, whereas the surgeon knows renal tuberculosis only as the destructive organ lesion. In other words the laboratory worker has been talking about an entirely different entity than the clinician.

The clinical picture of renal tuberculosis, unfortunately, has very few distinctive symptoms and usually not until the ureter and bladder become involved is attention focused in that direction. In any case of persistent bladder irritation, and especially in a young person, one must consider renal tuberculosis. It should be considered gross negligence not to investigate a patient who suffers with persistent frequency and dysuria. A careful check of the history charts on our cases revealed that 60 per cent of the cases with renal involvement presented some evidence of urinary disturbances surprisingly mild as compared to the pathological changes found. This fact must stand out boldly to all of us—and in private practice one must ever be alert and suspect genito-urinary tuberculosis until it is definitely ruled out. At Sea View with 1650 patients our routine procedure allows very few cases to escape our attention. All urines that reveal pus or blood are referred to the resident urologist even though the patient may give a completely negative genito-urinary history. Our diagnostic routine is to recheck the catheterized bladder urine with special attention directed to the isolation of tubercle bacilli. A flat x-ray plate of the genito-urinary tract is followed by intravenous urography using diodrast. In our experience intravenous pyelography is rarely of aid in detecting an early lesion, but is of decided assistance in the more advanced cases—which constitute a great majority that come under our observation. Cystoscopy with examination of the bladder and split urines for tubercle bacilli and renal function is carried out under caudal anesthesia—we employ 30 cc. of 2 per cent novocain. In a limited number of patients we have employed gas oxygen or spinal anesthesia with 50 mg. of neocaine. Intravenous evipal anesthesia for cystoscopy proved unsatisfactory due to frequent straining and tremors. Bilateral pyelo-ureterograms

are performed on all patients—up to the present time, in over 1500 cases, we have had no fatality or untoward reactions with the use of bilateral simultaneous pyelo-ureterograms. At the present time we employ hippuran for retrograde pyelography.

The coexistence of renal tuberculosis and nephrolithiasis is not common. Some authors consider the occurrence of renal tuberculosis and renal calculi as associated diseases, whereas



Fig. 62.—Bilateral retrograde pyelography. Early case of tuberculosis. Necrosis is limited to upper right calyx. Middle and lower calyces retain normal appearance. Left kidney normal.

others believe that such an association is unlikely. Our interest in this problem was aroused by the scarcity of cases of nephrolithiasis encountered at Sea View Hospital. During the past five years only six cases of renal calculi were brought to our attention. Of these, four were associated with renal tuberculosis. In a total of 1300 routine autopsies only two cases of renal tuberculosis associated with renal calculi were encountered. The incidence of calculi in tuberculous kidneys was placed by Tatnall at 1.4 per cent, by Howald at 1 to 1.4

per cent, by Olsen at 2.7 per cent and by Crenshaw at 1.8 per cent. According to Eisendrath, renal tuberculosis and calculi are associated in about 1.8 per cent. Our percentage of incidence is even lower and varies between 0.9 to 1 per cent.

The diagnosis of renal tuberculosis is made by the recovery of the organism from the segregated urine plus an



Fig. 63.—Right nephrectomized kidney. Case shown in Fig. 62 on section cortical abscess was found adjoining upper calyx.

alteration in the renal architecture as demonstrated by pyelography. The typical lesions are:

1. Cortical necrosis—"moth-eaten appearance" (Figs. 62, 63).
2. Irregular dilatation of the kidney pelvis (Fig. 64).
3. Obliteration of one or more calyces (Fig. 65).
4. Calyceal abscess (Fig. 66).
5. Stricture of the ureter (Fig. 65).

**Treatment.**—We believe that the patient with a non-destructive lesion should have sanatorium treatment. It is essential that the patient be kept under observation by both



Fig. 64.—Bilateral renal tuberculosis. Occlusion of upper end of ureter on right and tuberculous hydronephrosis with irregular dilatation of the pelvis and calyces on the left.



Fig. 65.—Bilateral retrograde pyelography. Tuberculous necrosis involving left upper calyx, upper segment of middle calyx and obliteration of lower calyx. Left tuberculous ureteritis and stricture

the medical and urological staffs. By a nondestructive lesion we mean a patient without urinary symptoms or changes in the pyelo-ureterograms. Such cases are referred to the urologist only because tubercle bacilli have been recovered in a routine urine and then recovered again from one kidney at the time of a urological survey. When the pathologist speaks of healed renal tuberculosis, we believe he refers to the above described case that frequently comes under our observation.

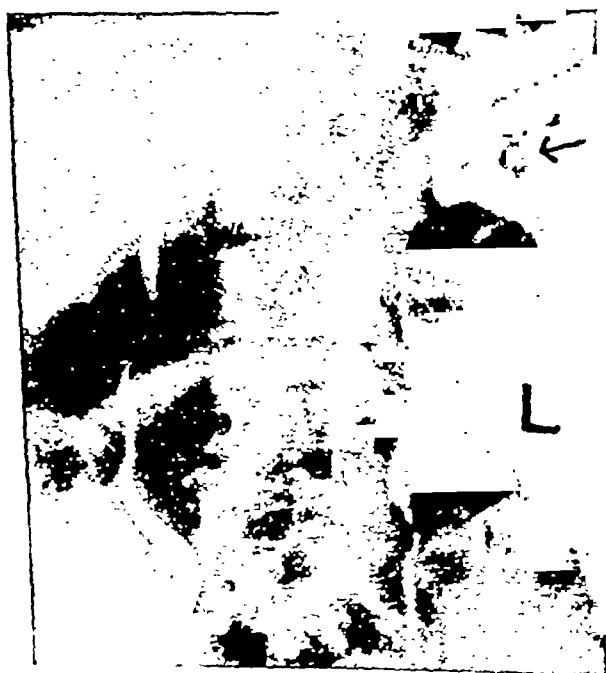


Fig 66—Bilateral retrograde pyelography. Nephrectomy revealed left middle calyceal tuberculous abscess.

It is quite natural to understand why we rarely, if ever, encounter this type of case in private practice. Some observers prefer the term preclinical tuberculosis of the kidney for this nondestructive lesion, which in our opinion either heals or progresses and becomes the true organ, destructive or chronic renal tuberculosis. We believe that all investigators in the entire field of tuberculosis agree that this type of renal path-



ology calls for surgical intervention. But one must not lose sight of the fact that by no surgical measure is it ever possible to remove all tuberculous tissue from the body, and any surgical procedure must be regarded as but one step in the cure of tuberculosis. All cases that present a destructive lesion are nephrectomized, or if the ureter is dilated, a nephro-ureterectomy is performed preferably under spinal anesthesia.

We feel justified with our results in performing a nephrectomy when a destructive lesion is present in one kidney and a nondestructive or very early lesion is present in the other

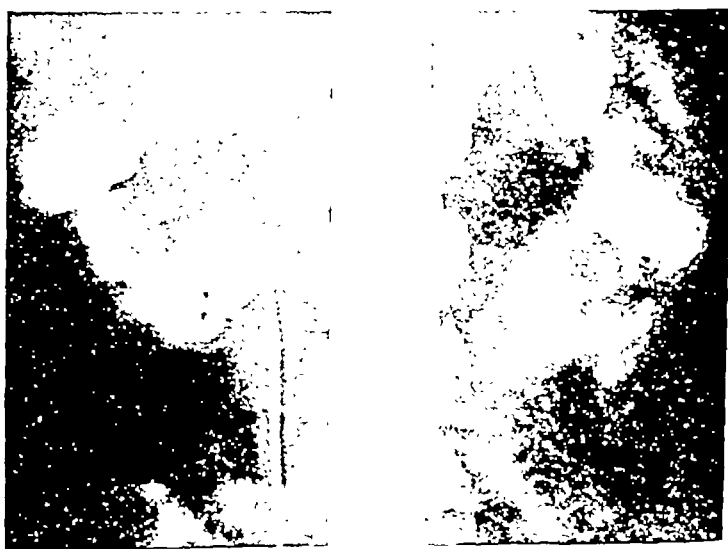


Fig. 67.—Advanced bilateral renal tuberculosis. Bilateral nephrostomy. (Patient alive two years after operation.)

kidney. Many of the patients on our service present advanced bilateral lesions—most of them are extremely miserable due to a coexisting ureteritis and bladder involvement. Such an individual in almost constant pain with frequency at five-minute intervals during the day and night presents a problem for medical and surgical management. Cystotomy with a permanent suprapubic tube offered no aid in many. Bilateral nephrostomy has been successful in affording relief (Fig. 67).

We have tried the direct application of ultraviolet radiation to the bladder and to the kidney through the cystoscope. The results in our hands have not been encouraging, and, in our opinion more harm than good is done by the latter procedure. All our cases receive general heliotherapy treatments—both pre- and postoperatively. Those who suffer with bladder symptoms postoperatively are usually improved with bladder lavages and general supportive treatment. Many cases of persistent bladder symptoms are due to an empyema of the ureteral stump; that is why we advocate nephro-ureterectomy.

We should like to go on record as answering some of the debatable questions regarding renal tuberculosis:

1. Can a kidney secrete or excrete tubercle bacilli and remain healthy?

It is our firm conviction that the presence of tubercle bacilli in the urine points to a lesion in the kidney.

2. Can a tuberculous lesion in the kidney heal? Yes, providing it is a nondestructive, miliary lesion and does not occur as a terminal hematogenous dissemination from an extensive organ tuberculosis elsewhere in the body. True clinical renal tuberculosis does not heal.

3. In bilateral renal tuberculosis should the more diseased kidney be removed? Yes—if an early lesion exists in the so-called “good kidney.”

4. Is the bladder picture of aid in diagnosis? In advanced cases only—early renal tuberculosis rarely presents bladder involvement.

#### GENITAL TUBERCULOSIS

The work of various authorities on tuberculosis of the genital tract in the male has by no means given us a clear-cut and well-defined picture of the condition from either the clinical or the pathological point of view.

It is agreed that the infection may reach the genital tract by way of the blood stream, lymphatics or by continuity of tissue. At the present time, there are two schools of thought on the pathogenesis of this condition. Hugh Young, the lead-

ing exponent of the radical school of treatment of genital tuberculosis, asserts that the seat of tuberculous involvement in the genital tract is in the seminal vesicles and that the prostate is involved in most instances. In a series of 342 urogenital cases reported by Young, it was found that the prostate was the single genital organ most frequently involved. Menville, in a survey of a group of cases at the Mayo Clinic also found that the prostate gland was the organ most frequently involved in tuberculosis of the genital tract in the male. Barney, Caulk, Hinman and many others believe that the epididymis is the seat of primary infection in the genital tract, and are of the opinion that the infection is hematogenous in origin. Cunningham in a review of 4250 necropsy records at the Boston City and Long Island Hospitals found 35 cases of tuberculosis of the epididymis in which gross and microscopic examination of the epididymis and gross examination of the prostate and vesicles were recorded. The vesicles were involved in 25 cases and the prostate was tuberculous in 25 cases. There were ten cases in which the epididymis alone was involved and because of this, he believes that the disease is primary in the epididymis. Barney and Hinman believe that if the prostate is involved first, the infection is secondary to renal tuberculosis which so frequently occurs together with genital tuberculosis.

In a survey of 666 autopsies performed on male patients at Sea View Hospital, tuberculosis of the genital tract was found in 67 cases. Genital tuberculosis occurs during the age of greatest sexual activity. In our group, the average age was thirty-nine years, with the ages ranging from two to sixty-seven years. The majority of the cases were white and this is commensurable with the fact that the ratio of white to colored autopsies at our institution is 2.5:1.

Primary tuberculosis of the genital tract is exceedingly rare. Many authorities believe that it does not exist. Koll, in 1915, reported a case of primary tuberculosis of the prostate. The prostate which was removed showed tuberculous involvement on gross and microscopic examination. There was no other evidence of tuberculosis elsewhere in the body.

In a review of the literature up to that time, he found two more cases of primary genital tuberculosis. We have never seen a case of primary tuberculosis of the genital tract. The difficulties attending the discovery of extragenital foci in many cases must always be borne in mind. It is generally believed that genital tuberculosis is secondary to some other focus in the body. This focus is most frequently found in the respiratory tract. Barney in a study of 154 cases of tuberculous epididymitis found tuberculosis of other parts of the body in 55.8 per cent. Involvement of the lungs was most common, 22.7 per cent. Bumpus and Thompson in a study of a series of cases of tuberculous epididymitis found extragenital tuberculosis in 54.8 per cent of cases. In our group of 67 cases there was clinical and roentgenological evidence of active pulmonary tuberculosis in all but five instances. Four of these five cases had bone tuberculosis and all of them had renal tuberculosis. On postmortem examination, pulmonary tuberculosis was found to be present in every case. The pulmonary disease was of the caseous pneumonic type in 77 per cent of the cases. In 3 cases fibrotic (healed) lesions were found. The remaining 12 cases showed nodular or miliary tuberculosis. There were 11 cases of tuberculosis of the spine, bones, and joints; and there were 8 cases of tuberculous meningitis.

It is extremely common to find genital and renal tuberculosis in the same patient, and in others while urinary tuberculosis cannot be proved, it is often suspected. In the diagnosis of genital tuberculosis, evidence of a tuberculous lesion in the urinary tract should be sought for.

Webb Johnson is of the opinion that the infection is carried by the urinary tract in most instances. Menville found renal tuberculosis in 77 per cent of his series of 65 cases of genital tuberculosis in the male. He feels that this justifies the belief that in the majority of cases, involvement of the genital tract is secondary to renal tuberculosis. In Bumpus and Thompson's series of 300 cases, renal tuberculosis was found in 110 cases. In 100 cases of genital tuberculosis, Thomson Walker found accompanying urinary tuberculosis in 37 cases. Camp-

bell believes that the pathogenesis of tuberculosis in the male genital tract with renal tuberculosis is different from that in cases without tuberculosis of the kidneys.

In the opinion of Campbell, genital tuberculosis without involvement of the kidneys is an hematogenous infection and starts in the epididymis, whereas the same with renal involvement reaches the genital tract by way of the urinary passages and the prostate and seminal vesicles are the first to be invaded.

In our series, we divided the cases into the two groups as suggested above. Out of our 67 cases, 51 or 76.1 per cent had renal involvement. The renal type of tuberculosis was subdivided into two groups. The ulcerative type, better known as the organ tuberculosis of the kidney, or the surgical kidney; and the miliary or nonsurgical kidney. Fourteen or 27.5 per cent of cases were of the organ type of renal tuberculosis. Only 3 of these cases were bilateral. The remaining 37 cases were of the nonsurgical or miliary type. Here on the other hand the majority of cases showed bilateral lesions.

It is interesting to know that 10 of the 14 cases of organ tuberculosis in the kidney were diagnosed antemortem by means of intravenous or retrograde pyelography. Although the urine was positive for tubercle bacilli in many instances, this alone could not be taken as an absolute indication of the presence of renal tuberculosis. These patients had tuberculosis of the genital tract and it was impossible to determine from which lesion the bacilli were derived. Another question to be considered is whether or not tubercle bacilli can be excreted in the urine without a definite lesion in the urinary tract. Fullerton and Hillier assert that in advanced pulmonary tuberculosis, bacilli may be excreted through the urinary tract without a tuberculous focus in that tract. It was not until recently that doubt has been thrown upon this concept by Menton, and only a short time ago by Medlar. Greenberger, Wershub and Auerbach surveyed a series of 500 cases at Sea View Hospital two years ago and their conclusions were similar to those derived by Medlar.

In the cases of coexisting renal and genital tuberculosis it

is extremely difficult to determine which lesion occurred primarily. The reason for this is that tuberculosis of the urinary tract may cause little or no symptoms, and so it becomes almost impossible to detect the duration of the disease with any degree of accuracy. The classical symptoms: frequency, nocturia, urgency and dysuria are common findings in tuberculosis of both the urinary and the genital tracts, and consequently cannot be of any great value in determining which one of these tracts is involved. In 2 of our cases there was involvement of an epididymis many years before the onset of either pulmonary or renal symptoms. In 1 case there was a history of gonorrhea and consequently it was impossible to ascertain whether the epididymitis was due to a tuberculous or gonorrheal infection. In the other case an epididymectomy had been performed but here, too, we were unable to find out the etiological factor for removal of the organ. The majority of authorities agree that an ascending infection from the genital to the urinary tract is extremely rare, and many urologists, including ourselves, say that they have never seen it.

In determining the frequency with which the various organs of the genital tract were involved, our survey disclosed some very interesting findings. The prostate gland was involved together with one or more of the other genital organs in 60 out of our 67 cases. Even more important is the fact that the prostate was the sole tuberculous involvement of the genital tract in 21 or 31.5 per cent of the entire group. Menville in his 65 cases found the prostate tuberculous in 86.4 per cent of cases. In no reported series of cases, however, was the prostate alone infected nearly as frequently as we found it to be.

We divided our cases into those with renal involvement and those without tuberculosis of the kidney. In our 16 cases with no gross or microscopic evidence of tuberculosis in the kidney we found the prostate gland involved in 14 or 87.5 per cent of these cases. In the other cases there was tuberculosis of the seminal vesicle in conjunction with other parts of the genital tract. In 3 of this group the prostate was the sole genital

organ involved. Therefore, we find that we cannot agree with Campbell, Barney, Hinman and others that the epididymis is the site most frequently involved in genital tuberculosis even in the absence of renal lesions.

The clinical diagnosis of tuberculosis of the prostate was made in about one third of the cases. If all of our cases had been thoroughly worked up by the urological department, we feel certain that the percentage of clinical diagnoses would have been much greater. The symptoms and findings of this condition are very varied indeed, undefined and not clear. Often the diagnosis can only be made late in the disease.

In our series the following clinical findings were most significant:

1. Enlargement of the prostate.
2. Irregularity and nodulation.
3. Asymmetry between the two lateral lobes.
4. Induration.
5. Boggiess and a fluctuant sensation usually on one side.
6. The prostate was not tender in the great majority of instances. In only 4 cases was tenderness experienced.
7. In 2 cases the prostate was definitely smaller than normal.

The great variation in the physical findings can be explained by the character of the pathology found at postmortem examination. Here again it may be wise to consider the ulcerative, and the nodular and caseous lesions as separate groups. There were 9 cases with definite ulcerations in the prostate. Eleven cases had firm, nodular, fibrotic prostatic lesions and in the remaining 40 cases there were areas of caseation present on gross and microscopic examination. In only 6 cases was one lobe of the gland involved. In 54 the lesions were diffuse and in 2 cases the prostate was almost completely excavated. The clinical and pathological description as to the location and type of tuberculous disease corresponded in 94 per cent of the cases.

The organ which was involved second in order of frequency was the epididymis. Tuberculosis of the epididymis in con-

junction with some other portion of the genital tract occurred in 30 or 44.8 per cent of our cases. It is of extreme importance to note that the epididymis as the sole organ of genital tuberculosis was involved in only 3 cases. In all of these instances there was extensive bilateral disease of the kidneys. In the majority of cases both epididymes were involved. The right epididymis was tuberculous more frequently than the left in the remaining cases.

The diagnosis of tuberculosis of the epididymis is frequently difficult to make. In a large number of patients with genital tuberculosis the only findings are limited to the epididymis, and therefore a careful differential diagnosis of tuberculosis of the epididymis must be considered. Of the conditions that must be ruled out, the most important are:

1. Lesions due to trauma.
2. Lesions of infectious origin:
  - (a) Gonorrhea with hydrocele.
  - (b) Lues of testes and epididymes.
3. Tumors of the epididymes:
  - (a) Angioma.
  - (b) Lipoma.
  - (c) Fibroma.
  - (d) Carcinoma.
  - (e) Dermoid.
4. Tumors of the spermatic cord:
  - (a) Lipoma.
  - (b) Fibroma.
  - (c) Sarcoma.
  - (d) Hematocele.
  - (e) Spermatocoele.
5. Tumors of the testicular tunics:
  - (a) Sarcoma.
  - (b) Fibroma.

Before making the diagnosis of tuberculous epididymitis in any acute lesion in the epididymes, certain other factors should be considered. The discovery of an extragenital tuberculous focus often makes the diagnosis certain.

In the majority of instances, the site of tuberculous infection in the epididymis is in the globus minor. Tuberculous epididymitis may start as an acute swelling with pain and en-



largement. There may be a hydrocele formed in some instances. This may mask the underlying pathology. In most instances there is enlargement of a portion of the epididymis. This is hard, irregular or nodular and only rarely painful or tender. In many cases focal suppuration or fluctuation may be recognized. The swelling of the epididymis is painful in about 50 per cent of cases. There may be draining scrotal sinuses which are extremely hard to close. In our series, scrotal sinuses were found in only two instances. The swelling of the testicle with or without tenderness, the presence of an enlarged thickened, nodular, indurated epididymis with or without draining sinuses, and a thickened and beaded vas were of greatest aid in making the diagnosis of tuberculosis of the epididymis. The important fact still remains that the discovery of a tuberculous lesion elsewhere was of greatest aid in making the diagnosis of tuberculous epididymitis.

The seminal vesicles were involved in 29 of our 67 cases, and were the only demonstrable tuberculous foci in the genital tract in three instances. Here as with the epididymis the involvement was bilateral in a great majority of cases. In the remaining cases the right seminal vesicle was involved much more frequently than the left. It will be recalled that the same condition was found to be true in tuberculous epididymitis.

The clinical diagnosis of tuberculous seminal vesiculitis is often difficult to make. Cunningham found that in many of his cases of tuberculous epididymitis, the lesions in the prostate and vesicles were not and could not be detected by rectal palpation.

With the available clinical material at our disposal, the diagnosis of tuberculous seminal vesiculitis was made in seven instances. The diagnostic features were thickening, induration, distention and enlargement. Vesiculograms were attempted in a few cases but failed to yield definite results. It was extremely difficult to visualize the vesicles.

The majority of authorities are of the opinion that tuberculous infection of the testis is always secondary to tuberculosis of the epididymis. Tuberculosis starting in the testis is ex-

tremely rare. The testis was infected in 15 cases of our group, but there was not a single instance where the genital involvement was present in the testis only. Both testes were involved in 8 cases, the right in 4 and the left in 3 cases. In most instances the disease was not extensive enough to be detected on physical examination. When signs were present the most prominent ones were irregularity, induration and adhesion.

The cases of multiple involvement of the genital organs were then investigated and several important facts were brought to light that are more graphically detailed in Tables 1 to 5.

A detailed examination of the various ways in which the genital tract was involved revealed that in unilateral lesions of the seminal vesicles, epididymes and testes, there was no evidence of cross infection. In other words, we found no cases in which, for example, the right seminal vesicle and the left epididymis were involved. Our findings agree with the contentions of others that cross infection in the genital tract is rare, and that in most instances involvement of the kidney and various organs in the genital tract occur on the same side.

The effect of gonorrheal infection on tuberculosis of the genital tract deserves some mention. Donges among others believes that nontuberculous infections of a genito-urinary tract may, in the presence of pulmonary tuberculosis, predispose to tuberculous involvement of the genito-urinary tract. The nontuberculous infection serves as a *locus minoris resistentiae* and as a result, tubercle bacilli accumulate there. Sixteen of our cases gave a clinical history of gonorrheal infection. All of these cases, except 1, had extensive pulmonary tuberculosis, and in all but 2 cases there was extensive renal tuberculosis. One case had tuberculosis of the vertebrae. In spite of the severe extragenital tuberculous involvement, 5 of these cases showed the prostate to be the only genital organ involved. In 1 case, only the right epididymis was infected while the remaining cases revealed extensive genital involvement. Thus there was no reason to believe that in our group

TABLE 1  
INVOLVEMENT OF PROSTATE, SEMINAL VESICLES, EPIDIDYMES AND TESTES

	No renal disease.	Right kidney.	Left kidney.	Both kidneys.	Total.
1. Prostate, both seminal vesicles, both epididymes and both testes.....	..	..	..	4	4
2. Prostate, right epididymis, both seminal vesicles and both testes.....	..	..	..	2	2
3. Prostate, left epididymis, both seminal vesicles and both testes.....	..	..	..	..	0
4. Prostate, both epididymes, both seminal vesicles and right testis.....	..	..	..	1	1
5. Prostate, both epididymes, both seminal vesicles and left testis.....	..	..	..	1	1
					8

TABLE 2  
INVOLVEMENT OF PROSTATE, SEMINAL VESICLES AND EPIDIDYMES

	No renal disease.	Right kidney.	Left kidney.	Both kidneys.	Total.
1. Prostate, both seminal vesicles and both epididymes.....	1	..	.	1	2
2. Prostate, right seminal vesicle and both epididymes.....	..	..	..	2	2
3. Prostate, right seminal vesicle and right epididymis.....	1	1	..	..	2
4. Prostate, left seminal vesicle and left epididymis.....	..	..	1	..	1
5. Prostate, both seminal vesicles and right epididymis.....	1	..	..	1	2
					9

TABLE 3  
INVOLVEMENT OF THE PROSTATE, EPIDIDYMES AND TESTES

	No renal disease.	Right kidney.	Left kidney.	Both kidneys.	Total.
1. Prostate, both epididymes, both testes.....	..	1	..	..	1
2. Prostate, both epididymes, left testis.....	..	..	..	1	1
3. Prostate, right epididymis, right testis.....	1	..	..	1	2
					4

TABLE 4  
INVOLVEMENT OF THE PROSTATE AND EPIDIDYMES

	No renal disease.	Right kidney.	Left kidney.	Both kidneys.	Total.
1. Prostate and right epididymis.....	1	..	..	..	1
2. Prostate and left epididymis.....	1	..	..	1	2
					3

TABLE 5  
INVOLVEMENT OF THE PROSTATE AND SEMINAL VESICLES

	No renal disease.	Right kidney.	Left kidney.	Both kidneys.	Total.
1. Prostate and both seminal vesicles.....	1	..	..	5	6
2. Prostate and right seminal vesicle.....	1	..	..	1	2
					8

the preexisting gonorrheal infection served as a predisposing factor in the invasion of the genital tract by the tubercle bacillus.

We believe that a few words concerning therapy will not be amiss. It was maintained previously that there are two distinct schools of thought with reference to this condition. The exponents of radical surgery, led by Hugh Young, believe that excision of the entire genital tract is the treatment of choice. The reason for this treatment is the belief that the disease arises in the genital tract in the prostate and vesicles, and that from these foci the bacilli may involve any other portion of the tract. The radical operation has, however, introduced an immediate postoperative mortality which in the experienced hands of Young, himself, reached 4 per cent in one of his series.

The advocates of more conservative therapy, namely, Barney, Hinman and others, believe that the epididymis is the primary seat of infection in the genital tract. They therefore recommend epididymectomy with ligation of the vas high up on the affected side, and a prophylactic ligation with removal of a small portion of the vas on the opposite side. They maintain that a large number of persons are rendered sterile by genital tuberculous involvement so that ligation of the opposite side should be done without hesitation. Even in the face of involvement of the prostate and seminal vesicles the conservative school, to which we subscribe, continues to recommend epididymectomies and removal of infected portions of the testis leaving apparently healthy testicular tissue behind. After epididymectomy the prostatic lesions often tend to retrogress and become cicatrized. Supportive measures including heliotherapy, tuberculin and small doses of x-ray have been advocated by some. We prefer heliotherapy and rest as supportive treatment.

The prognosis of genital tuberculosis in the male is not very good regardless of the type of surgery employed. The course following operative interference depends to a large ex-

tent on the nature of the tuberculous process or processes elsewhere in the body. Several cases have been reported in which a rapid generalized miliary tuberculosis with terminal tuberculous meningitis developed shortly after operative interference. We have never noted such a course following surgery.

The rate of recurrence after surgical procedure is about 40 per cent. In Bruns' series of 111 cases there was recurrence in 60 per cent of the unilateral cases from three to thirty-four years after operation. Barney in 49 cases of unilateral lesions observed recurrence on the opposite side of 37 per cent of cases within three years following epididymectomy and orchidectomy. Bumpus and Thompson found a recurrence of 39 per cent in the opposite side within one year after operation.

## SUMMARY AND CONCLUSIONS

### RENAL TUBERCULOSIS

1. Renal tuberculosis is blood-borne.
2. Renal tuberculosis is usually associated with pulmonary tuberculosis—it is never primary.
3. The nondestructive, closed or miliary renal lesion is common and is bilateral in more than 80 per cent.
4. The destructive, open, organ, or chronic surgical tuberculosis of the kidney is usually unilateral—is notably deficient in symptoms which are explained by the absence of involvement of the ureter and bladder.
5. The diagnosis of renal tuberculosis rests on the recovery of the tubercle bacilli, plus alterations in the renal architecture as demonstrated by retrograde pyelography.
6. The presence of tubercle bacilli in the urine means that a lesion exists.
7. Treatment of the clinical, organ, open or destructive renal lesion, is always surgical.
8. The miliary, closed or nondestructive renal lesion should be treated medically—this type lesion may heal, but calls for close cooperation and observation by the urologist and internist.

9. The coexistence of renal tuberculosis and nephrolithiasis varies between 0.9 and 1 per cent in our series.

#### GENITAL TUBERCULOSIS

10. Tuberculosis of the genital tract was found in 67 or 10.1 per cent of our series of male autopsies. This figure compares favorably with those reported by other investigators.

11. The average age for the group is 39.8 years. This figure is a little higher than those reported by most authorities.

12. There was extragenital tuberculous disease found in every case.

13. Renal tuberculosis was present in 76.1 per cent of the cases.

14. The prostate gland was the single genital organ most frequently involved. From the standpoint of frequency the epididymis, seminal vesicles and testicles were infected in the order named.

15. Tuberculosis of the prostate gland as the sole involvement of the genital tract was present in 31.5 per cent.

16. The symptoms and diagnostic features of tuberculosis of the various genital organs were reviewed and a comparison of the clinical and pathological findings was made. In some cases the clinical data were not sufficient for the proper diagnosis.

17. Our findings agree with those of Bumpus and Thompson that in most instances involvement of the kidney and various organs in the genital tract occurs on the same side and that cross infection is rare.

18. The effects of a preexisting gonorrheal infection on tuberculosis of the genital tract were studied. Although most of our cases showed extensive bilateral involvement, our results were such that we could not find any relationship of the gonorrheal to the tuberculous infection.

19. The observation of other investigators that more than 30 per cent of the victims of genito-urinary tuberculosis succumb to miliary tuberculosis and tuberculous meningitis was not encountered in our series.

20. We believe the treatment of genital tuberculosis should be conservative. We do not subscribe to the radical surgical removal of the genital tract.

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## CLINIC OF DR. M. KOVNAT

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#### PREGNANCY AND TUBERCULOSIS

IN 1935 Ornstein and the author<sup>1</sup> reviewed the course of 85 pregnant women suffering with tuberculous pulmonary disease. The study was prompted by the lack of any guiding indications in the management of this complication and the apparent undercurrent of pessimism in its outcome. This pessimistic attitude dates back to Ortega<sup>2</sup> with short periods when the prognosis veered to the opposite extreme. In general, the reports from early investigators indicate a deleterious effect on the disease in 33 to per cent of the cases. Kaminer<sup>3</sup> reports bad results in 50 per cent of his cases, Merletti<sup>4</sup> 50 per cent, Lempert<sup>5</sup> 75 per cent, Von Rosthorn<sup>6</sup> 75 per cent, Von Bardeleben<sup>7</sup> 71 per cent, Reiche<sup>8</sup> 77 per cent, Parry<sup>9</sup> 50 per cent and Bacon<sup>1</sup> reports 33 per cent of deaths in the first year.

As the data of our cases were being collected, it appeared as though the prevailing pessimistic outlook in such cases was justified, but when the facts were entirely assembled and analyzed, a different aspect presented itself. The 85 cases studied at Sea View Hospital had an average stay in the institution before confinement of two and one-tenth months and after delivery, of three months. Of the 85 cases 31 or 36 per cent died, 15 or 18 per cent were unimproved or showed progression of their pulmonary disease and 39 or 40 per cent were improved. At first glance these figures which show 54 per cent of the cases progressed or died appeared to follow the results of the other investigators and revealed a generally poor

prognosis for this complication. When these figures, however, were compared with a large group of females from the same institution, uncomplicated by pregnancy, the results of the pregnant group did not show up unfavorably. In the nonpregnant group of 5470 admissions, 1850 or 33 per cent died, 1696 or 31 per cent were unimproved and 1969 or 36 per cent improved. In this group of nonpregnant females, therefore, 64 per cent died or had a progression of their disease. These two groups were comparable in practically every respect, sources of admission into the institution, their age, the extent and character of the pulmonary pathology and the management employed in their treatment.

The analysis of the final outcome in the 85 pregnant cases yielded no clue as to how the individual patient would be affected by the complication, until each case was studied individually in respect to the character of its own pulmonary pathology. The qualitative classification devised by Ornstein, Ulmar and Dittler<sup>11</sup> was employed. In this classification the tuberculous pulmonary pathology is grouped into three divisions: the resolving exudative and exudative productive form; the chronic productive form, and the malignant caseous-pneumonic form of the disease. The following case reports illustrate this classification and the course of the disease in each group.

**The Resolving Exudative Form.**—S. R., age twenty-one, gravida I, was admitted to the institution December 3, 1932, with a history of loss of weight, slight cough and fatigue and a six weeks' pregnancy. Physical examination revealed a white female, poorly nourished, but not appearing acutely ill. Over the right anterior chest, there was dulness, bronchovesicular breathing and many moist râles. The sputum was negative. The x-ray, taken on December 5, 1932, revealed a homogeneous density over the right upper lobe and a similar but less extensive shadow in the left infraclavicular region. With routine rest treatment, the cough subsided and the physical signs diminished. On August 26, 1933, the patient had a normal, spontaneous delivery. An x-ray taken on September 21, 1933, revealed resolution of the exudative process. On September 28, 1933, she was discharged as an arrested case, free of all symptoms. In retrospect, this patient went through an uneventful pregnancy, confinement and puerperium while taking a successful rest cure for her exudative productive pulmonary tuberculosis.

This case illustrates the resolving exudative form of the disease. It is an acute process and the lesions vary from a lobule to an entire lobe. The reaction is chiefly serous with some fibrin and cellular elements. There is little or no destruction of tissue. Resolution may therefore occur without leaving a trace or with a few fibrotic strands as evidence of previous infection. In the benign exudative group where the dose of bacilli is small and the tissue sensitivity high, resolution may occur in from six weeks to six months. In the exudative-productive form, because of some fibrin and cellular deposits, resolution takes a longer time. The prognosis is uniformly good in this form of the disease particularly with proper rest treatment.

There were 9 such cases in our study. There were no deaths in this group; 7 were discharged from the hospital improved, 2 were discharged as unimproved. In a later follow-up of these cases, 6 were traced. None of these had died nor was there any evidence of reactivation of the disease.

**The Chronic Productive Form.**—L. E., age twenty-three, gravida II, was admitted to the institution on April 12, 1933, with a history of cough and hemoptysis dating back to one year previously and a pregnancy of four months' duration. Physical examination revealed a white adult female, appearing fairly well nourished and not acutely ill. The physical signs in the chest were scanty, occasional fine râles elicited over the right upper lobe. Subjectively, the patient had few symptoms. The sputum on admission was positive, Gaffky 3. The x-ray on April 12, 1933, revealed proliferative changes in the right infraclavicular region. Her course while in the hospital, was entirely uneventful except for continued gain in weight and a return of negative sputum from June until her discharge in October. On September 6, 1933, she had a normal spontaneous delivery. An x-ray on September 26, 1933, revealed the same proliferative changes in the right infraclavicular region with apparently no change from the time of her admission. On September 28, 1933, she was discharged as apparently arrested. In retrospect this case likewise went through a normal pregnancy, confinement and puerperium with no effect on her pulmonary disease other than the usual improvement noted with routine rest care in this form of pathology.

This case illustrates the chronic productive type. The reaction of this form is chiefly cellular and acinous in distribution. The process usually begins in the apex, and slowly

spreads through the lungs. There are few symptoms of toxemia. The prognosis likewise is usually good in this form of tuberculosis. This form of pathology usually occurs where tissue sensitivity is low and dosage of tubercle bacilli is small. There were 25 cases of this type. No deaths occurred during their stay in the hospital. Twenty-three were discharged as improved and 2 as unimproved. In a later follow-up study, 14 of these cases were traced. Two of these had further slow progression of their disease as sometimes occurs in this form and ultimately died. Their deaths both occurred about one year after the delivery. One of these had been originally discharged as unimproved. The remaining 10 cases have apparently had no reactivation of their lesion and are still considered as arrested cases.

**The Caseous-pneumonic Form.**—G. B., age twenty-four, gravida III, was admitted to Sea View April 4, 1933, with a history of pulmonary symptoms dating back six months previously. Physical examination revealed a poorly nourished adult white female with extensive physical signs through the right lung. The sputum was negative on admission. An x-ray taken on April 5, 1933, revealed a caseous-pneumonic lesion involving the right upper lobe with a marginal pneumothorax which was initiated at the previous institution a short time before. The patient, however, refused to cooperate and resisted further refills. The sputum soon after turned positive. On July 7, 1933, she went through a spontaneous normal delivery. Clinically her condition continued to go downhill. An x-ray on September 25th, revealed further extension of the pathology in both lung fields. The patient's condition continued to grow worse and she died on November 15, 1933.

In reviewing this case we note a rapid progression of the disease, ending in the death of the patient four months after confinement. In this form of tuberculous disease there is high tissue sensitivity and large dosage of bacilli. The reaction is severe, with resultant death of tissue. There is both caseation and necrosis. Following liquefaction of the whole mass the dead tissue is sloughed out, resulting in cavity formation, the chief characteristic of this form of the disease. The prognosis in this form is uniformly bad, and improves only as it lends itself to closure of the cavity. In the case cited above the

patient gave up her only opportunity for recovery when she refused to continue her pneumothorax.

Our original study contained 51 cases of this form of the disease. Thirty-one died, 10 were discharged as unimproved and 10 were discharged as improved. In a later follow-up of the 20 discharged cases, 6 had died. In order to determine whether the pregnancy was responsible for the unusually high mortality, a group of 51 nonpregnant females suffering with the similar caseous-pneumonic form of the disease was studied. In this group there were 23 deaths, 25 showed progression of their disease, and only 3 were improved. The only apparent difference was the speed with which the condition progressed. In the pregnant group the average duration of life was two and one-tenth months. In the nonpregnant group it was ten and three-tenths months.

From the impressions gained as a result of this study a working formula was laid down to guide the staff in the management of this complication in the individual case. In brief, it advised the attending physician to expect no deleterious effect in the exudative-productive and chronic productive forms of the disease. In the caseous-pneumonic forms, active therapeutic measures for closure of cavities, so essential in all such cases, was all the more imperative in the pregnant females, if an early exitus was to be avoided.

We have had an opportunity to test this formula in 59 cases admitted to Sea View subsequent to the original study above cited. Thirty-five were of the caseous-pneumonic form, 14 the exudative productive, and 10 chronic productive. Fifteen died on the average of two months after the delivery. They all belonged to the caseous-pneumonic group. Fifteen were unimproved or progressed. These were all likewise from the latter group of 35. There remain 5 of 35 caseous-pneumonics that did not show progression of their disease. One had her disease arrested by means of thoracoplasty subsequent to her confinement. Another was a pneumothorax case with a good collapse of the diseased process. Another had an initial collapse instituted two months prior to her delivery

and continued after her discharge. A fourth had a thoracoplasty before her pregnancy.

Of the remaining 14 exudative-productive and 10 chronic productive cases none died nor showed any aggravation of their condition after their delivery and puerperium. They were discharged on the average six months after their confinement.

We are now doubly convinced, both from our original study, and the subsequent observations, that the proper qualitative diagnosis and classification of the type of pulmonary pathology will determine the course of the disease when complicated by a pregnancy. We reiterate, the exudative-productive and chronic productive forms have the usual favorable prognosis, regardless whether we are dealing with or without this complication. In the caseous-pneumonic form the appearance of a pregnancy is only another indication for hastening all active measures to close the cavity. If this can be accomplished the complication will not interfere with the patient's improvement and an ultimate arrest of the disease. If it cannot, the usual progression of the disease in this form will be hastened and an early exitus a frequent occurrence.

I wish to thank Dr. H. Katzev for aid in compiling the data.

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## CLINIC OF DR. ISRAEL G. EPSTEIN

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#### FLUOROSCOPY AND x-RAY IN PNEUMOTHORAX THERAPY

RIGHTFULLY, collapse therapy is at present the greatest weapon at our disposal in the treatment of the caseous-pneumonic form of pulmonary tuberculosis. Of the collapse procedures, the pneumothorax while simple as to technic and attended with comparatively slight risk and morbidity, has been called upon more and more of late in the attempt to control the tuberculous cavity.

Physical examination although very valuable and informative, has its limitations. The percussion note with its extent of hyperresonance does not give the examiner a true picture as to the extent of lung collapse. The diminution of breath sounds may be deceiving particularly when there is a column of air completely surrounding a partially collapsed lung with a patent cavity. The coin sound, when obtained correctly, may map the edge of the collapsed lung. However, when one uses this procedure on a number of cases, he soon realizes the shortcomings of this test.

The fluoroscopy and x-ray examination is an invaluable aid in the course of pneumothorax therapy for here we have a visual picture of the lung that is undergoing collapse treatment. For the sake of clarity, the course of pneumothorax therapy may be divided into four periods. The first, before collapse therapy is instituted; the second, the primary pneumothorax with its initial refills; the third, the pneumothorax maintenance; the fourth, the period of reexpansion of the collapsed lung. If these four periods are carefully controlled roentgen-

ologically, a more intelligent, safe, and comfortable pneumothorax is likely.

#### THE PERIOD BEFORE COLLAPSE THERAPY IS INSTITUTED

Physical findings when positive are important in the recognition of the caseous-pneumonic form of pulmonary tuberculosis. The deep-seated cavity or the one with a good deal of compensatory emphysema may give no or scant physical findings. Frequently a large solitary cavity can be seen over which area no altered breathing or râles are heard. The localization of the pathology is important and a record should be kept by means of an *x-ray* film. Throughout the entire course of treatment an attempt will be made to keep the pathological portion well collapsed with less attention paid to the part of the lung free of cavitation. A record, by means of the *x-ray*, is kept of the condition of the lung prior to the institution of collapse therapy. This is compared with the picture of the re-expanding lung when the time is thought to be propitious for lung reexpansion. Stereoscopic *x-rays*, anteroposterior, postero-anterior, lateral views of the chest as well as fluoroscopy are used in determining the extent, character and position of the pathology in the involved lung.

#### THE PRIMARY PNEUMOTHORAX

A primary pneumothorax is done with the initial refills. After the first few treatments, a visual picture is necessary to determine the location of the instilled air and the lung edge. The collapse of healthy lung tissue with no effect on the diseased lung tissue is undesirable. A successful pneumothorax is one that compresses the pathological portion of the lung. At this time, the character of the collapse is noted and the decision whether to continue pneumothorax treatments is made.

#### THE PERIOD OF PNEUMOTHORAX MAINTENANCE

A visual appraisal of the extent of collapse is obtained before and after each pneumothorax inflation. From this information, one could estimate the amount of air necessary to

control the diseased portion of the lung. From the extent of collapse before a refill, one can infer the amount of air absorbed from the last treatment to the present one when one keeps in mind the fluoroscopy picture of the position of the collapsed lung after the last inflation. In this way one may most accurately judge the amount of air necessary at each treatment and the interval of time between inflations.

If the lung is free, the excavated portion of the lung may collapse to a greater extent than the uninvolved portion. This may be due to the loss of tissue in the caseous-pneumonic lung with poor aeration and partial atelectasis (Ornstein) or to the atelectasis caused by a more complete stenosis of the bronchus to the lobe as a result of the shifting of the lung by the pneumothorax (Coryllos). When this selective collapse of the involved portion of the lung is observed under fluoroscopy, one could easily keep the uninvolved portion reexpanded to a great extent by varying the amount of air given at each refill. In this way, a control of the tuberculous lesion is obtained while the healthy portion retains its function. This is more important when bilateral collapse therapy is attempted. Here the vital capacity is low and the margin between comfort and discomfort is narrow. A conservation of normal lung tissue is important, obtained only by careful roentgenological control. No bilateral pneumothorax therapy should be attempted without the facilities of repeated roentgenological examinations.

The comfort of the patient must be considered during pneumothorax treatment. A mediastinum pushed over to the contralateral hemithorax does not exert sufficient pressure on the pathology. A fixed mediastinum against which the pathological lung may be pushed is to be sought. An accurate appraisal of the flexibility of the mediastinum can be obtained only on a careful fluoroscopy when changes of position of the mediastinum could be observed on inspiration and expiration. The maximum shift is noted in the anteroposterior position upon expiration. In the expiratory phase, in the presence of a mobile mediastinum, the heart and mediastinal contents shift

markedly to the contralateral side. Constant fluoroscopy and x-ray examinations before and after pneumothorax refills are necessary to keep the mediastinum in the midline to promote fixation in that position. A good deal of the dyspnea of which pneumothorax patients complain may be traced to a mobile mediastinum with too great a shift of the heart and mediastinal contents to the contralateral thorax.



Fig. 68.

It is generally admitted today that in only 40 out of 100 cases in which pneumothorax is attempted, is satisfactory collapse of the lung obtained. In 10 per cent, the pleural cavity is found completely obliterated and in 50 per cent adhesions are present preventing closure of cavities (Coryllos). These bandlike formations, attached to the visceral and parietal pleura are often sufficient to prevent the pathological portion of a lung from collapsing. The adhesions are not always visible in the orthodox x-ray positions. An x-ray of the chest in the expiratory phase is an aid in bringing out the extent and char-

acter of the adhesive bands. In this position, the maximum lung collapse could be visualized rendering the adhesions more taut. We have found x-rays of the chest taken in lordotic position of great aid in determining the extent, thickness, direction and attachments of adhesive bands. With these x-rays, one can determine to a great degree the advisability of attempting to sever these pleural bands.

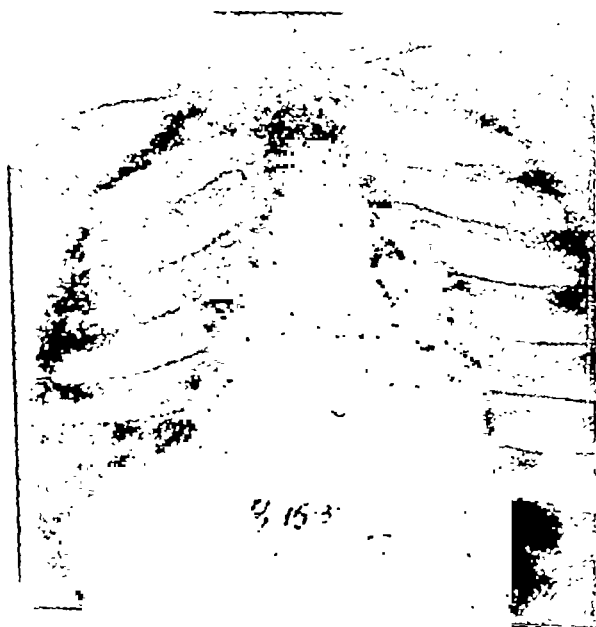


Fig. 69.

Figure 68 is an x-ray demonstrating a pneumothorax of the left chest with the pathology not collapsed completely. A cavity is still seen patent in the midportion of the uncollapsed lung. Suggestion of adhesions is seen but none can be traced clearly.

In the lordotic position, four distinct adhesion bands can be traced as indicated in Fig. 69. These were confirmed on thoracoscopy when the surgeon's drawing almost completely coincided with the x-ray picture.

Figure 70 is an x-ray taken ten weeks later. Dr. P. N. Coryllos has severed all the adhesions seen on the lordotic

x-ray. The pneumothorax was then more effective in securing a complete collapse. The cavity seen in the first figure could not be visualized.

The technic of lordotic x-rays is simple. A preliminary fluoroscopy is done, the best visualization of the adhesion bands is sought by placing the patient in the anteroposterior and postero-anterior lordotic position. The curve of the body is noticed and then reproduced in taking the x-ray. The x-ray

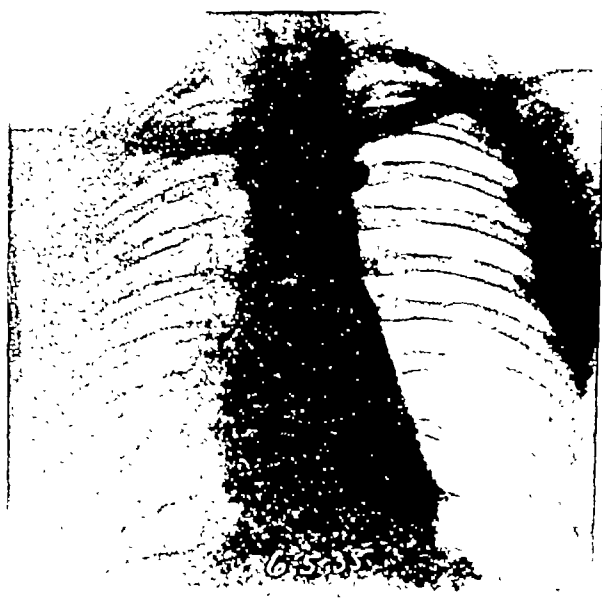


Fig 70

tube is placed high and angulated to cause sufficient distortion to bring out more clearly the adhesion bands.

Roentgenograms of the thorax in the lateral and oblique positions are useful in determining the extent of an irregular collapse. When one gets into difficulty with an irregular collapse or a reexpanding lung, fluoroscopy in the oblique positions marking the near point over the pneumothorax pocket, enables one to obtain the point at which the pneumothorax

needle should be inserted. In this way a reexpanding pneumothorax may be maintained and vascular accidents avoided.

In the presence of fluid, a visualization of the collapsed lung is comparatively difficult. X-Ray pictures may be taken with the patient lying on the uninvolved side thus allowing the fluid to gravitate toward that side and the midline of the body. The edge of the collapsed lung is therefore exposed and a



Fig. 71.

proper visualization of the lung edge obtained. A film with the patient lying on the involved side may also aid in visualizing the extent of lung collapse under accumulated fluid.

Figure 71 is an x-ray of a patient who developed fluid in the right thorax during the course of pneumothorax therapy. The edge of the collapsed lung could not be clearly traced. Therefore the extent of lung collapse could not be accurately observed.



Figure 72 is an x-ray of the thorax of the patient shown in Fig. 71 taken in the anteroposterior position. She is lying on her right side. The fluid gravitated downward exposing the collapsed lung. The entire lung edge could be traced with ease.

A proper fluoroscopic and x-ray control is very necessary during the course of pneumothorax therapy. By this visual

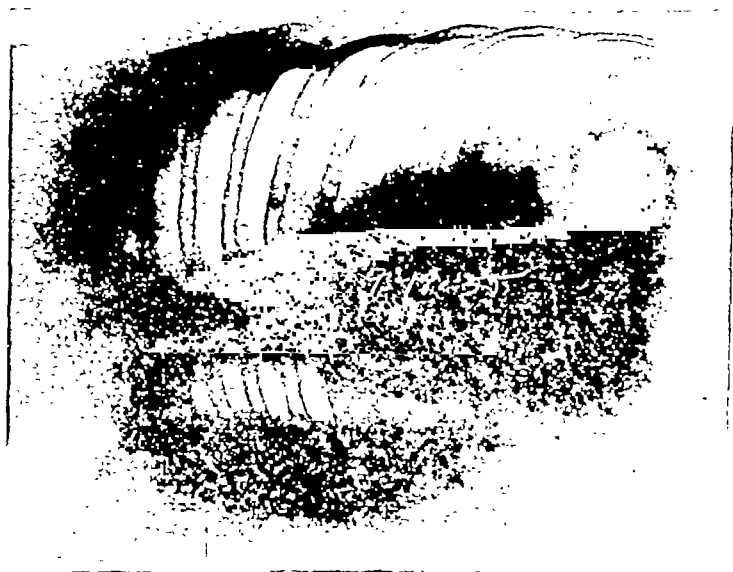


Fig. 72.

check, one is able to judge the efficacy of the treatment, the amount of air to be given at each inflation, the interval between treatments, and the control of both adhesions and complicating fluid.

#### THE PERIOD OF REEXPANSION OF THE COLLAPSED LUNG

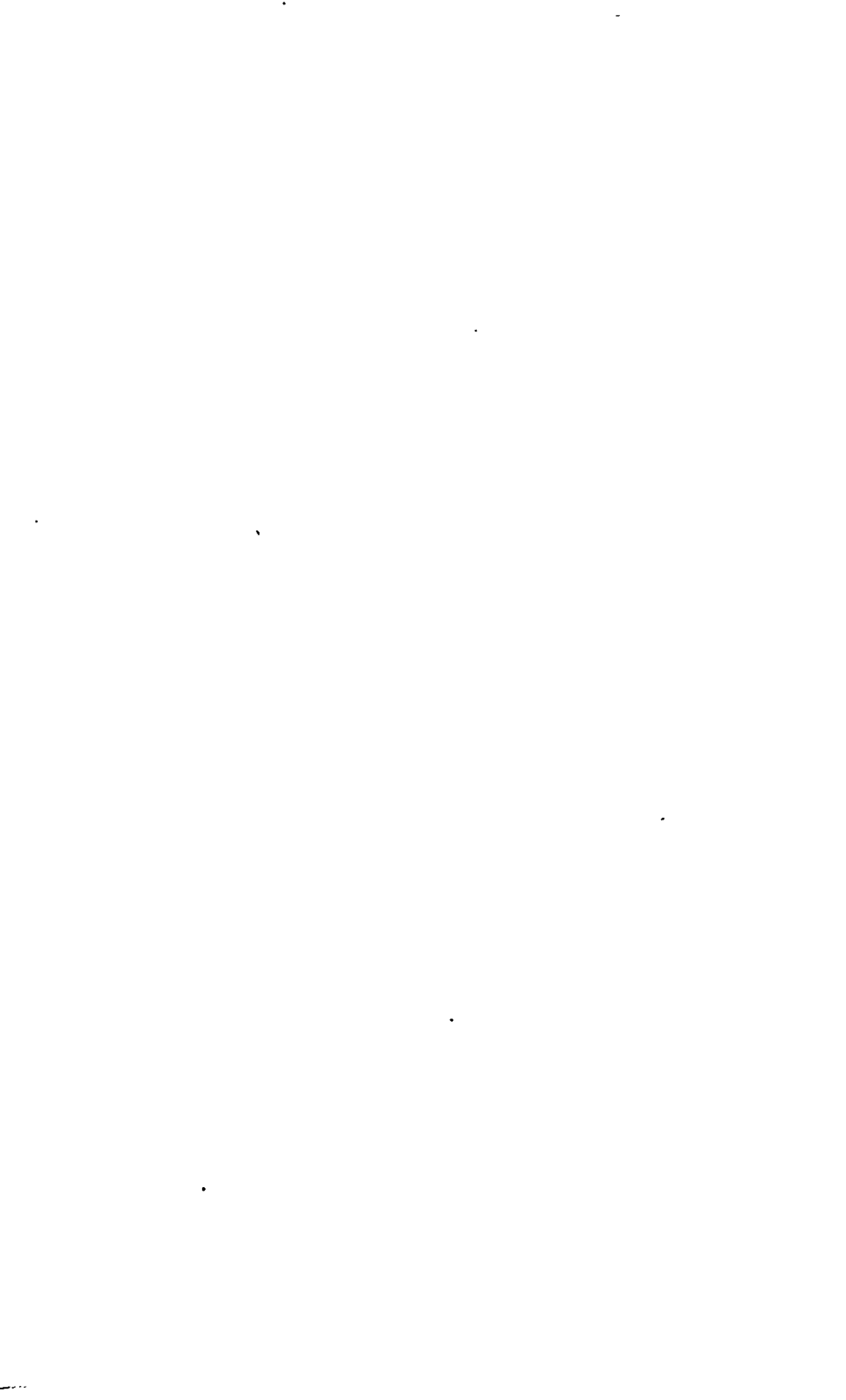
After a sufficient period of pneumothorax therapy, the lung is allowed to reexpand. Repeated fluoroscopic and x-ray examinations reveal no open lesions in the collapsed lung, the sputum examinations demonstrate no tubercle bacilli. The lung is allowed to slowly reexpand under frequent roentgenological examinations. If the lesion in the involved lung seen

prior to pneumothorax therapy is completely healed, the lung is allowed to approach the thoracic wall and become adherent. Shadows seen in the reexpanding lung are compared with corresponding areas in the involved portion prior to treatment. Small effusions, folds in the pleura and scar tissue may be confusing. A close check is necessary to reassure the physician that no open lesion exists.

An atelectatic lung may not reexpand fully so that the mediastinum is drawn over to the same side as the air is absorbed. This in turn causes an emphysema of the other lung in an effort to fill the enlarging hemithorax. Under fluoroscopy and x-ray this is observed and steps taken to correct this condition.

#### SUMMARY

The importance of fluoroscopy and x-ray in pneumothorax therapy is discussed. Frequent roentgenological control is important in every stage of pneumothorax therapy. At times, x-ray and fluoroscopy in different positions are necessary to keep the lung and pneumothorax in view. x-Rays taken in the lordotic position help in the visualization of adhesions preventing good lung collapse.



## CLINIC OF DR. S. EDWARD KING

FROM THE METABOLIC SERVICE, SEA VIEW HOSPITAL AND MEDICAL SERVICE, NEW YORK POSTGRADUATE HOSPITAL

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### THE TREATMENT OF DIABETES COMPLICATED BY TUBERCULOSIS

**Introduction.**—The coexistence of diabetes and tuberculosis in the same patient introduces special problems which do not exist in either disease alone.

Tuberculosis tends to develop in diabetics who have neglected their condition for long periods. Most patients are of fairly advanced age, necessarily so, since the incidence of diabetes is low under forty.<sup>1</sup> In Root's<sup>2</sup> series of 245 tubercular diabetics, about 50 per cent were over fifty years of age. Similarly about 75 per cent of our cases were forty-five years or older. Such individuals are very liable to suffer from the sequelae of uncontrolled diabetes, namely, vascular sclerosis and coronary disease. These are important complications which markedly affect the treatment and prognosis of tubercular diabetics. Possibly they also influence the pathology of the pulmonary infection and its symptoms.

It is the general rule for this group to present mild forms of diabetes. Severe cases are comparatively rare and are confined to the younger age groups and to those with endocrine disorders. Only 15 per cent of our cases could be classified as severe diabetics, and of these more than half were thirty years of age or younger. The frequent history of antecedent coma is not necessarily an index of severity, but rather of inadequate or total lack of control of the diabetes.

The pulmonary condition in the majority of tubercular diabetics is usually first recognized at an advanced stage of

the disease. This is true not only in municipal hospitals and clinics, but also in private practice. This situation in itself materially influences the ultimate prognosis of these cases.

It is difficult to account for this unfortunate situation. Most authorities do not believe that pulmonary tuberculosis in diabetics differs materially in its course or clinical signs from that in other patients. If this is so, the explanation is attributable to indifferent diagnosis and failure of those treating diabetes to appreciate the relative frequency of this complication.

Malnutrition is frequently present at the time of hospital admission, particularly in the poorer economic groups in whom diagnosis and treatment of both diseases are delayed. Anorexia, vomiting and laryngeal involvement may interfere with food ingestion and treatment.

**Indications and Objectives of Diabetic Treatment.**—The immediate indication is to control the diabetes as quickly as possible, while insuring adequate nutrition and weight increase to the estimated normal. The diabetic control must be constant, for even short periods of glycosuria are detrimental to the pulmonary disease.

The general objectives are in no way different from those in ordinary cases of diabetes; namely:

1. Elimination of ketosis and acidosis.
2. Elimination of glycosuria.
3. Treatment of dehydration.
4. Readjustment of body weight and nutrition.
5. Estimation of permanent carbohydrate tolerance and corresponding adjustment of insulin and diet (stabilization).
6. Control of blood sugar, cholesterol, chlorides, etc. (when possible).

**Methods.**—(A) Diet.

1. *Calories.*—Total calories are calculated from the normal weight and present nutritional status. The appetite, degree of physical activity, presence of fever or toxemia, influence caloric requirements considerably. Even under similar con-

ditions, individuals differ vastly, in their caloric requirements. The total caloric intake must be so adjusted as to permit gain in weight and improvement in nutrition when necessary, the goal being an approximately normal body weight. There is no particular virtue in increasing the body weight much above normal, since obesity has no influence upon the pulmonary disease, but has a distinctly undesirable effect upon the diabetes. Depending upon individual indications, from 1800 to 2500 calories are usually prescribed.

2. *Carbohydrates*. — Moderately high carbohydrate diets<sup>3, 4, 5, 6</sup> are now generally employed in the treatment of diabetes. Such diets prove more palatable, and within limitations probably stimulate carbohydrate tolerance. They are also of value in preventing hypoglycemia in cases taking insulin. Nor is much more insulin required than with the former high fat diets.<sup>3, 5</sup>

McCann<sup>7</sup> has objected to high carbohydrate diets in pulmonary tuberculosis upon the theoretical assumption that the greater CO<sub>2</sub> formation and increased pulmonary ventilation, aggravates the pulmonary pathology. No clinical evidence to confirm this hypothesis has been observed.

3. *Protein*. — It is our practice to employ a fairly, but not excessively high, protein quota; about 90 Gm. daily. There are theoretical objections to the use of high protein diets, adverse effects upon carbohydrate tolerance being reported.<sup>1, 8, 9</sup> However, the amounts here employed are not sufficiently high to produce any objectionable effect.

There are many reasons why an adequate protein diet must be prescribed in severe cases of tuberculosis. As previously shown,<sup>7, 10</sup> protein requirements in tuberculosis are greater than normal. This is due to fever, toxemia, increased nitrogen destruction, as well as loss of protein through various channels. Unless this negative balance is prevented, anemia, cachexia, and edema are prone to develop.

4. *Fat*. — High fat diets are undesirable from many points of view. Fatty foods prove unpalatable to individuals confined to bed and suffering from poor appetite. Fats delay

the disease. This is true not only in municipal hospitals and clinics, but also in private practice. This situation in itself materially influences the ultimate prognosis of these cases.

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4. *Fat.*—High fat diets are undesirable from many points of view. Fatty foods prove unpalatable to individuals confined to bed and suffering from poor appetite. Fats delay



gastric evacuation and may produce indigestion and vomiting. High fat diets appear to definitely diminish sugar tolerance.<sup>1</sup>

For these reasons, the older high fat diets are now rarely used. Sufficient fats are prescribed to bring the diet up to caloric requirements.

5. *Accessory Substances and Minerals*.—Adequate amounts of the accessory food substances are provided by the inclusion of fresh fruit juice, cereal, butter, milk, fruits and green vegetables in the diet daily. In our experience, vitamin B furnished as yeast or in various proprietary products, often exerts a stimulating effect upon appetite and promotes gain in weight.

Adequate calcium, phosphorus, and iron is obtained by the inclusion of milk and fresh vegetables in the daily menu.

6. *Food Distribution*.—Carbohydrates are usually distributed in about equal proportion among the three meals with the noon meal slightly lower in carbohydrate, but higher in protein and fat. When supper is eaten early, as is customary in institutions, it is advisable to serve one glass of milk at night to tide over the long fast, or if preferred, a fruit or dessert. A small amount of carbohydrate is also frequently prescribed in the forenoon. This procedure seems to be of value in preventing excessive fluctuations in blood sugar, particularly when much insulin is used, and also probably exerts a mild stimulating effect upon carbohydrate tolerance for the following meal.

**Diet Prescriptions.**—The following diets are employed on the metabolic service at Sea View Hospital:

<i>Diet.</i>	<i>Carb.</i>	<i>Prot.</i>	<i>Fats.</i>	<i>Calories.</i>
Low carbohydrate. . . . .	100	90	160	2050
Medium carbohydrate No. 1. . . . .	130	90	100	1700
Moderate carbohydrate No. 2. . . . .	150	90	120	1950
High carbohydrate No. 1. . . . .	200	90	110	2050
High carbohydrate No. 2. . . . .	250	90	120	2400

**Insulin.**—This hormone has radically altered the treatment and prognosis of diabetics with tuberculosis. It is now possible to quickly desugarize the diabetic without restricting

the diet. Its use is indicated in all cases of diabetes not easily controlled by moderate carbohydrate restriction, and especially where malnutrition is present. In these cases, insulin should be employed without delay to permit assimilation of a high caloric diet.

There are no valid contraindications to the use of insulin. Focal pulmonary reactions<sup>11, 12</sup> first reported were probably due to protein impurities. Although insulin reactions occasionally occur, there is no evidence that such reactions exert any disastrous effect upon the pulmonary disease.

The customary procedure for the administration of insulin is followed. Severe diabetics require two or three injections, the larger one before breakfast to check the high blood sugar usually present at that time. The smallest dose is given before lunch. In very severe cases of diabetes, a small injection is often necessary at night about 9 P. M. to check the rising blood sugar during the night and early morning hours. The recently introduced modifications of insulin with retarded absorption and prolonged effect may reduce the number of required injections in such cases.

The total insulin dosage varies with the severity of the diabetes ranging from 10 units in very mild cases to about 150 in very severe instances. One refractory case required as much as 400 units daily. Young diabetics and those with endocrine disorders of the thyroid, pituitary and sex glands are the most difficult to control, and require the largest amounts of insulin.

Because of vagaries of appetite and food intake, it is not desirable to administer more than 30 or 40 units of insulin at one time, lest hypoglycemic reactions occur. In cases requiring large and frequent doses of insulin, it is advisable to follow the sequence of events closely by sugar determinations of postprandial urine specimens. This reveals the efficiency of the individual dose of insulin, in relation to the available carbohydrates in each meal. Glycosuria means that the insulin has not been effective in preventing the blood sugar from rising above the renal threshold (usually 160 to 180 mg. per 100 cc.). It therefore indicates either an increase of insulin

or a reduction in the carbohydrate content of the individual meal. In many instances, glycosuria occurs only during part of the day and can only be localized by divided urine examinations.

Local insulin reactions occasionally occur, but are seldom severe and usually disappear spontaneously or when another brand of insulin is substituted. They are allergic manifestations which must not be confused with true insulin reactions or hypoglycemia. Crystalline insulin, free of protein impurity, is now available for such cases.

**Hypoglycemia.**—Hypoglycemic insulin reactions are frequent in tubercular diabetics. This is due to various causes, of which the following are the most frequent:

1. Tubercular patients suffer from marked variations in appetite, as well as frequent gastro-intestinal upsets. Lack of ingestion of the expected quota of carbohydrate may precipitate hypoglycemic reactions especially if large amounts of insulin are being used.

2. The average mild diabetic on proper treatment undergoes a progressive improvement in carbohydrate tolerance that is often astonishing. Unless this natural change is recognized and anticipated by reduction in insulin, or increase in the carbohydrate intake, insulin reactions may supervene.

3. Patients who have previously been confined to bed may develop hypoglycemic reactions due to the improved carbohydrate tolerance resulting from increased muscular activity.

It has been stated previously that insulin reactions do not exert any obviously injurious effect upon the pulmonary tuberculosis. This does not mean, however, that hypoglycemia is without danger. On the contrary, a sharp reduction in blood sugar is distinctly dangerous, particularly in middle-aged individuals with coronary sclerosis and myocardosis, as emphasized by Levine,<sup>13</sup> Sherrill<sup>14</sup> and others.

The treatment of hypoglycemia consists in the administration of fruit juice or dextrose, syrup by mouth, as soon as the premonitory symptoms—sweating, giddiness, diplopia, etc.,

develop. Unfortunately, the symptoms are extremely variable, and the condition may not be recognized until the individual is in coma. In such instances, glucose intravenously and adrenalin are urgently necessary.

**The Blood Sugar.**—Very little consideration has been given so far in this discussion to the blood sugar level as a criterion of satisfactory control of diabetes. Although a more accurate gauge of conditions than the urine, the blood sugar has proved of limited practical value. This is due to the impracticability of obtaining frequent blood sugar determinations and the necessary delay in receiving the results of these analyses from the laboratory. Urine specimens, however, can be collected without difficulty and the sugar determined immediately.

For practical purposes, the blood sugar is of little clinical value as long as glycosuria persists. Glycosuria in a proved case of diabetes is sufficient evidence of a high blood sugar (at least over 160 mg.). Only when glycosuria disappears is the blood sugar level of any clinical value. Fasting morning specimens, or postprandial blood sugar determinations may then be used to gauge the efficacy of treatment. Progressive reduction in blood sugar suggests improvement, while continued increase indicates diminishing tolerance preceding glycosuria.

Much controversy has centered upon the significance of persistently elevated blood sugar levels without glycosuria. Most investigators, including Mosenthal<sup>15, 16, 17, 18</sup> and MacLeod<sup>19</sup> do not believe that elevated blood sugar levels without glycosuria, are in themselves dangerous or responsible for the symptoms, sequelae, or complications of diabetes. Nor is there any proof that blood or tissues of increased sugar content favor the growth of organisms or are less viable<sup>20</sup> or resistant to infection than normal.<sup>21</sup> The lowered local and general resistance of uncontrolled diabetes is probably attributable to the desiccation and perverted tissue metabolism of this disease.

It follows that although a relatively normal blood sugar, especially in younger people, is desirable, this objective must

not be made a fetish to the detriment of the patient. Especially in older people, a moderate hyperglycemia (without glycosuria) is harmless,<sup>18</sup> and probably necessary<sup>22</sup> and excessive efforts to lower it must be avoided.<sup>14, 23</sup> Strouse<sup>24, 25</sup> observed cardiac symptoms, including fibrillation, block and angina following the reduction of previously elevated levels of blood sugar. Due to a high renal threshold, older diabetics frequently exhibit no glycosuria, with fasting blood sugar levels of 200 mg. or over.

**Acidosis.**—Severe acidosis is rarely seen except in young diabetics; slight degrees of ketosis may develop in mild diabetics due to intercurrent infection, gastro-intestinal upset, or in the presence of an acute pulmonary episode, especially hemoptysis.

In such cases, all other treatment becomes secondary until the ketosis and acidosis have been corrected. Frequent injections of insulin should be given, checked by urinary sugar and acetone determinations. If signs of ketosis persist, but glycosuria disappears, then insulin and glucose should be given intravenously. Fluids are forced by all channels to overcome the marked dehydration.

Not infrequently, diabetic patients seen for the first time in acidosis and coma are later found to be suffering from tuberculosis. The importance of acidosis in predisposing to subsequent pulmonary tuberculosis has already been emphasized.

**The Influence of Pulmonary Tuberculosis Upon Diabetic Tolerance.**—Tuberculosis appears to be an exception to the general rule that infections lower sugar tolerance in diabetes. Often, chronic tuberculosis exerts no appreciable effect upon the course of diabetes.

Many clinicians have noted the apparent benign influence of extensive progressive tuberculosis upon sugar metabolism in diabetes.

Joslin<sup>1</sup> states that when the diabetes is apparently improving, but the patient doing poorly and losing weight, suspect tuberculosis. Naunyn,<sup>26</sup> and others,<sup>27</sup> have reported instances

of distinct improvement in sugar tolerance of diabetic patients suffering from advanced tuberculosis. Lundberg<sup>28</sup> postulated secretion of an insulin-like hormone (para-insulin) by tuberculous tissue. It seems likely, however, that more tangible factors account for this effect.

1. In many instances, the changes noted appear to be no more than the normal increase in carbohydrate tolerance occurring in diabetics following desugarization and stabilization.

2. In severe terminal cases of tuberculosis, the explanation probably lies in the associated malnutrition. As emphasized by Allen,<sup>29</sup> undernutrition in itself exerts a decidedly beneficial effect upon carbohydrate tolerance. Prior to the introduction of insulin, undernutrition was a recognized method of treatment in diabetes. Marked improvement in sugar tolerance is very frequently observed in advanced or terminal cases, but inanition, weight loss, and restricted food intake, are invariably present. Many cases previously requiring large doses of insulin to prevent glycosuria, become sugar free without any insulin. True instances of improved tolerance due to advancing tuberculosis, without inanition, are rare. Only one case that may fit in this category has been noted on our service in the last five years.

It is not always true, however, that extensive pulmonary tuberculosis is without effect upon the carbohydrate tolerance. Glycosuria often appears in diabetic patients, following hemoptysis and extensive pulmonary or hematogenous spread, especially if associated with toxemia and elevated temperature. Such cases may pass quickly into acidosis or coma. Pleural effusions, sterile or purulent, often exert a deleterious effect upon sugar metabolism.<sup>30</sup> In some instances on our service, this complication was suspected because of unexplained glycosuria.

#### **Treatment of Pulmonary Tuberculosis in Diabetes.—**

No attempt will be made to cover this aspect of the subject which is exhaustively dealt with elsewhere. The usual indications for treatment of pulmonary tuberculosis apply. Age and frequency of vascular and coronary disease are the main

modifying factors that restrict application of surgical procedures. The fact that 85 per cent of pulmonary lesions discovered in diabetics are at an advanced stage, also necessarily modifies therapeutic indications and prognosis.

Probably the best results from surgical measures such as pneumothorax and thoracoplasty, are obtained in young diabetics, despite the severity of the associated diabetes. The reason is obvious, since such individuals have had less opportunity to develop general arteriosclerosis and other complications that are frequent in older diabetics. Often the status of the cardiovascular system in older diabetics precludes any surgical intervention whatsoever. Pneumothorax sometimes causes severe anginal symptoms in individuals with coronary sclerosis, and occasionally congestive cardiac failure has been noted. Dyspnea and orthopnea are frequent in cases with coronary sclerosis when extensive bilateral pulmonary involvement limits vital capacity.

**Prognosis.**—At one time the association of diabetes and tuberculosis was considered an invariably fatal combination.<sup>31, 32</sup> The introduction of insulin has markedly altered the immediate prognosis.<sup>33, 34, 35</sup> The diabetes can be controlled without great difficulty and very few cases die from that alone. The improvement in nutrition that follows insulin and an adequate diet favorably influences resistance to the pulmonary infection. Given a relatively early pulmonary infection, the prognosis in diabetics differs little from that in other patients.<sup>36</sup>

Unfortunately most cases of pulmonary tuberculosis in diabetes are seen at a relatively advanced stage of the disease. The problem involved is the treatment of a middle-aged group of individuals, usually with extensive pulmonary tuberculosis, and often suffering from the sequelae of poorly controlled diabetes; namely, vascular and cardiac disease. As long as the diagnosis of pulmonary tuberculosis is made at a very advanced stage of the disease in diabetics, the prognosis will remain poor. The immediate life expectancy following diagnosis

has probably been materially improved by modern methods of treatment.

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#### TUBERCULOUS EMPYEMA: A PRELIMINARY OUTLINE ON THE FORM OF TREATMENT EMPLOYED ON THE SURGICAL SERVICE OF THE SEA VIEW HOSPITAL

THORACIC empyema, which frequently follows lobar or bronchopneumonia, and empyema complicating pulmonary tuberculosis, present two entirely different clinical pictures.

In the former, we as a rule entertain no misgivings relative to the favorable outcome of the infection in uncomplicated cases. Generally, we are dealing with a pleural space in which the lung has been completely expanded until the advent of the pleural effusion, which, as it increases in volume, causes compression and displacement of the lung, heart and mediastinum.

If one were to slowly aspirate the purulent effusion, at the same time preventing air from entering the pleural space, the lung, owing to its elasticity, would expand as the effusion was withdrawn and at the end, would again fully return to its normal position.<sup>1</sup>

In tuberculous pyogenic empyema, we are confronted by a more serious problem which presents a vastly different and a more dismal clinical picture than does the usual postpneumonic empyema. Its successful treatment has been one of the most baffling combats with which the thoracic surgeon has had to deal

Before thoracic surgery became one of the great factors in the treatment of pulmonary tuberculosis, patients afflicted with tuberculous pyogenic empyema were operated upon by costectomy, followed by the insertion of a large drainage tube several inches in length. Purulent drainage continued for months or

years and recovery was of rare occurrence, even in patients with arrested lesions and negative sputum. This type of operation alone was in itself sufficient to prevent sterilization of the pleural cavity.

Once the thoracic cage is opened and a drainage tube inserted, secondary infection is a constant factor. If the patient did not succumb from active spreading tuberculosis, he died from a progressive generalized amyloid disease as a result of prolonged chronic sepsis.

The apparent hopelessness of these patients stimulated thoracic surgeons to exhaust every means in an effort to sterilize the pleural cavity and thus effect a cure. Various dyes were employed as well as gomenol in oil. Sterile filtered ox bile was also one of the many substances added to the list of remedies which were injected in quantity into the infected pleural cavity.

Today, if costectomy with simple drainage was employed, it would offer no brighter prognosis than in the earlier periods, unless an effort was made to reduce the toxemia by frequent irrigation of the empyema cavity, and to build up the patient with frequent blood transfusions to a point where, by thoracoplasty or Schede's operation, an attempt could be made to obliterate the cavity and cure the empyema.

It is the general opinion that to cure an empyema, whether tuberculous or postpneumonic, we must first be rid of the empyema cavity.

#### CLASSIFICATION

We cannot fully present the subject of tuberculous empyema without first discussing so-called "simple" tuberculous empyemas. These patients remain on the medical service under the care of the medical director and his staff.

Aspiration is not done unless the patient becomes embarrassed by accumulation of the effusion which may be sterile on culture but reveals tubercle bacilli on stained smears.

All pyogenic tuberculous empyemas admitted to the surgical service were at one time included under the simple form.

Mixed infection empyema may result from:

1. Contamination from without during paracentesis.
2. Tuberculization of needle tract followed by fistulization.
3. Spontaneous pneumothorax with bronchial fistula.
4. Empyema necessitatis with discharging sinus.
5. Rupture of a tuberculous cavity into the pleural space following a closed pneumolysis (Jacobaeus). Rupture of a tuberculous excavation into the pleural cavity is generally followed by a fetid anaerobic empyema.

### TREATMENT

At Sea View Hospital certain fixed rules have been promulgated for the treatment of tuberculous empyema.

All such patients when transferred to the surgical service are individualized and treatment accorded as may fit each one.

Patients with simple tuberculous empyema and *bronchial fistula* with no evidence of pyogenes either by culture or stained smear of the pleural effusion are recommended for thoracoplasty.

These patients sooner or later will develop a pyogenic tuberculous empyema and an early thoracoplasty will forestall this complication with its associated toxemia.

When the presence of a bronchial fistula is suspected and before any type of operative treatment is instituted, a small quantity of methylene blue solution is injected in the pleural cavity and the sputum examined during the next forty-eight hours for the presence of the dye.

Occasionally patients are admitted to the empyema service with a temperature ranging between 99° and 103° F. Exploratory thoracentesis reveals an extremely thick exudate from which no growth is obtained on culture, but when a stained smear is examined, numerous tubercle bacilli are found, together with a moderate number of unidentified organisms which may be anaerobes, but not of the group that are found in putrid empyema or lung abscess.

Treatment of these cases consists in placing the patient in a sitting posture and inserting an aspirating needle on the an-

terior axillary line through an interspace corresponding to the lowest point of the empyema cavity. After all of the thick exudate has been aspirated, the cavity is then thoroughly irrigated through the needle with warm normal saline solution, until the return washings are clear.

When this is accomplished, the patient lies down with the affected side uppermost, and from 200 to 450 cc. of 1:3300 azochloramide solution is injected in 50 cc. quantities through the needle into the pleural cavity. As the fluid level rises, air is displaced through the needle while the syringe is being refilled. The needle is then withdrawn and the puncture wound covered with collodion. This procedure is repeated daily for from seven to ten days. The temperature usually falls to normal in from forty-eight to seventy-two hours.

About one week later a needle is again inserted into the previously treated cavity and a small amount of fluid aspirated for examination. Stained smear reveals no tubercle bacilli or other bacteria and the effusion is either a clear amber color or a slightly cloudy, thin fluid.

Two patients among those recently treated by this procedure presented an empyema necessitatis, one patient revealing two anterior and one posterior fluctuating areas which were very painful on pressure.

Following treatment by aspiration at only one point on the anterior axillary line, plus azochloramide instillation, the fluctuating areas rapidly disappeared and were no longer a factor.

Because of the presence of organisms noted on direct smear in addition to tubercle bacilli, we have placed these patients in the class with mixed infection empyemas.

The reason for so doing is that occasionally a patient does not respond to the aspiration and instillation treatment and a closed thoracotomy is then performed.

All of our cases of mixed tuberculous empyema receive this treatment which consists in inserting a No. 18 or 20 mushroom catheter by means of a trochar and cannula, through the eighth or ninth intercostal space, employing local anesthesia. The anterior axillary line is selected in order that the

thoracotomy wound will not be near the line of incision if thoracoplasty is later performed.

After the catheter has been withdrawn until the tip is in contact with the parietal pleura, a Harloe empyema disk is then slid over the tube until it reaches the skin. The disk is then fastened to the skin by adhesive plaster.

**Postoperative Treatment.**—*Empyema without Bronchial Fistula.*—The catheter is connected by means of a glass Y tube to two 4-foot lengths of rubber tubing, one of which leads to a graduated irrigating bottle suspended from a stand beside the bed and filled with the irrigating solution (saline, azochloramide or chlorazene solution). The other tube passes into a bottle containing a small quantity of water to act as a water seal. The bottle is placed on the floor. The distal end of the second tube is connected to a 12-inch piece of glass tubing which passes through a 2-hole rubber stopper so that the lower end of the tube lies beneath the surface of the water for the distance of  $\frac{1}{2}$  inch.

As the fluid in the bottle rises, the glass tube is elevated so that the tip will not reach too far beneath the fluid level.

Every four hours the empyema cavity is irrigated, while the patient is supported in the sitting posture.

First, the outflow tube is compressed, and when the clamp is removed from the inflow tube, irrigating solution in 100 cc. quantities is permitted to alternately flow into the pleural cavity and thence into the bottle on the floor. This is continued until the return washings are clear. The inflow tube is then clamped and the outflow tube permitted to remain open.

During irrigation, the weight of the column of fluid in the outflow tube extending from the Y tube to the surface of the fluid in the bottle on the floor, exerts sufficient negative pressure to completely remove all washings from the empyema cavity.

The above postoperative treatment is modified to fit the individual case.

*Pyogenic Tuberculous Empyema with Bronchial Fistula.*

—No intermittent irrigation with negative pressure, as above described, is done.

The catheter instead is connected to a piece of rubber tubing about 2 feet long, the distal end of which passes into a liter bottle fastened to a side bar of the bed so that it hangs just below the level of the mattress. No water is placed in the bottle. The tube is left open at all times and at the end of every four hours the catheter is disconnected from the outer tube and 100 cc. quantities of warm saline solution are injected into the pleural cavity and then permitted to run out by gravity into a basin. Instillations are continued until the washings return clear. The catheter is again connected to the second tube so that further drainage between irrigations passes into the bottle.

If the saline solution was withdrawn with the syringe, instead of being permitted to flow out by gravity, the negative pressure occasioned by traction on the piston is likely to cause alternate opening and closing of the fistula, thereby delaying healing.

Postpneumonic empyemas managed in this fashion permit healing of the bronchial fistula in from six to fifteen days.

*Anaerobic Tuberculous Empyema.*—These patients are desperately ill and frequently become cyanotic and dyspneic immediately following rupture of the tuberculous cavity as the result of tension pneumothorax caused by a ball-valve action at the site of the ruptured cavity, which permits air to enter the pleural cavity on inspiration but prevents its exit. When confronted with such complications, the case becomes emergent and relief must be speedily administered.

The set-up for a closed thoracotomy must be made ready. In the interval, a large caliber aspirating needle should be inserted under local anesthesia, into the pleural cavity above the fluid level, to relieve any intrathoracic tension that might be present.

The needle should not be removed until everything is in readiness to insert the tube. Too long an interval between removal of the needle and insertion of the thoracotomy catheter

will result in a recurrence of tension pneumothorax. At this time, however, air and anaerobic pus will be forced into the needle opening recently made in the parietal pleura, causing a diffuse subcutaneous emphysema and resulting in a phlegmonous cellulitis of the chest wall, with possibly fatal termination.

The technic of closed thoracotomy and postoperative treatment for the anaerobic empyema, is the same as described under "Empyema with Bronchial Fistula."

Because of the extreme toxemia following anaerobic empyema, irrigation at four-hour intervals with 50-cc. instillations of warm normal saline solution, is most important. The relatively small quantity of saline employed does not enter the bronchus, particularly if the patient is supported in a high Fowler position. Not only does frequent irrigation cause thinning of the pus and favor drainage, but in addition it keeps the pleural cavity cleaner, thus reducing to a great extent absorption of toxins.

The disagreeable foul odor of the pus may in part be overcome if Dakin's sodium hypochlorite solution is placed in the bottle which is tied at the side of the bed to receive the drainage.

Further treatment consists in giving daily intravenous glucose and saline and a blood transfusion of from 250 to 400 cc. every fourth or fifth day.

Postpneumonic empyemas with bronchial fistula and anaerobes rapidly recover when treated in the above manner. The tuberculous patient, if promptly treated, should in a very short time overcome the anaerobic infection and be included in the list of pyogenic empyemas with bronchial fistula.

The treatment of mixed infection tuberculous empyema having been outlined, the question now arises as to whether, by the application of such treatment, the patient continues to improve and finally arrives at a point where, without further treatment, the empyema is cured.

As previously stated, no pyogenic tuberculous empyema is cured while the empyema cavity still exists.



**Thoracoplasty.**—The treatment by thoracotomy and irrigation is only the preliminary step. The next step is to eradicate the cavity by a two- or three-stage thoracoplasty. Every effort is made to treat the empyema at its inception and continue thereafter by systematic irrigation and supportive treatment to improve the general condition of the patient, to the point where he is a safe risk for thoracoplasty.

If one were to wait several weeks or months before attempting thoracoplasty, the continued irritation resulting from the infection within the pleural cavity would cause the pleura to become densely thickened, so that a Schede operation might be necessary.

Thoracoplasty must be done at as early a stage as the condition of the patient will permit. Many patients are thus cured.

If the final result is a small superficial discharging sinus, we should feel that much has been accomplished in what would have been in the earlier days a hopeless situation.

It is unfortunate that a large number of patients have extensive bilateral lesions and many are retrogressing. When empyema is added to such an apparently hopeless picture, a thoracotomy with supportive treatment is carried out, but all efforts fail to arrest the caseous-pneumonic pathology and these patients rapidly succumb.

There is, however, a less unfortunate group of patients with bilateral lesions, some of which are being controlled by selective pneumothorax.

A pyogenic empyema superimposed upon one or the other side, would of necessity require a longer period of treatment. Thoracoplasty would be contraindicated until such time as the lesion in the contralateral lung could be controlled by artificial pneumothorax, a selective pneumothorax being continued as outlined by Coryllos and Ornstein<sup>2</sup> in the management of bilateral tuberculosis.

In many patients the added sepsis of an empyema changes an apparently favorably progressing course to a rapidly changing down-hill course, finally ending in death.

Even in unilateral caseous-pneumonic tuberculosis complicated by pyogenic empyema, it is at times impossible by any means to improve the general condition of the patient or to arrest the parenchymal tuberculous activity in the involved lung, so that thoracoplasty might come to his aid.

#### SUMMARY

1. Pyogenic tuberculous empyema is a frequent and dismal complication of pulmonary tuberculosis.

2. All cases should be given the benefit of early thoracotomy.

3. With no contraindications, thoracoplasty should be performed as soon after the onset of the empyema as possible.

4. Patients with simple tuberculous empyema and bronchial fistula should receive thoracoplasty before they are complicated by mixed infection.

5. All cases of pyogenic tuberculous empyema with bronchial fistula, either aerobic or anaerobic, should be operated upon by thoracotomy with open tube and receive saline irrigation every four hours.

6. Frequent blood transfusion is by far the best therapeutic agent to improve the general condition of the patient before operation.

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## CLINIC OF DRS. IRVING GRAY AND IRVING GREENFIELD

FROM THE DEPARTMENT OF MEDICINE, SEA VIEW HOSPITAL

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### GASTRO-INTESTINAL SYMPTOMS IN PULMONARY TUBERCULOSIS\*

GASTRO-INTESTINAL symptoms in patients with pulmonary tuberculosis may be due either to functional disturbances, or organic changes in the alimentary canal. Pyrexia, disturbance of the vegetative nervous system, and emotional factors all play a part in the production of gastro-intestinal symptoms. When these factors come into play, we have the disturbance on a functional basis. Gastro-intestinal symptoms may occur in patients with pulmonary tuberculosis based on reflex mechanisms before there is any organic change in the intestinal tract. Abdominal symptoms due to ulcerative processes in the intestinal canal by the tubercle bacillus are rather frequent.

**Literature.**—The association between digestive disturbances and pulmonary tuberculosis has long been known. Brown and Sampson, who have contributed much of interest and importance to this subject, divide the history of intestinal tuberculosis into four periods.

1. "The dysentery period during which it was noted that diarrhea frequently occurred late in the course of pulmonary tuberculosis, but little consideration was given to the fact that it might be due to the same disease in a different organ. This, the period of clinical observation, extended from the time of Hippocrates to that of Bayle (1810).

\* We are indebted to Dr. Oscar Auerbach, Pathologist, at the Sea View Hospital for his cooperation

2. "The period of 'tuberculous diarrhea,' during which the lesions in the intestine were described and noted as tuberculous and the diarrhea definitely connected with them. This period of pathological observation extended from the time of Bayle (1810) to the time of Louis and Rokitansky (1825-1842).

3. "The period of pathological study during which the pathological changes were fully described and attempts made to connect the varying symptoms with the various changes in the lesions found at postmortem. The diagnosis during life was always uncertain. This period of pathological study lasted from the time of Louis and Rokitansky to 1919.

4. "The period of 'roentgenological diagnosis,' during which the diagnosis and consequently the scientific study and scientific treatment of intestinal tuberculosis could be accurately pursued, dated from the roentgenological diagnosis of intestinal tuberculosis and was placed on a firm foundation in 1919, by the work of the above authors at the Trudeau Sanitarium."

We have been interested in correlating the physical examination and clinical symptomatology with the findings on postmortem examination. At this clinic session, we desire to bring to your attention the predominant clinical symptoms and the findings on physical examination in correlation with the autopsy findings in a comparative study of 100 patients who died of pulmonary tuberculosis. For this study we have selected 100 consecutive records of patients who have died at the Sea View Hospital and we have analyzed the pathological protocols and the clinical charts. The Sea View Hospital is a municipal hospital for tuberculosis and all those eligible for free service, irrespective of color, creed or nationality, are admitted.

#### CHART 1

##### INCIDENCE OF PULMONARY TUBERCULOSIS IN RELATION TO AGE

	White.		Colored.	
	Male.	Female.	Male.	Female.
Incidence.....	37.0	25.0	20.0	18.0
Average age.....	40.7	23.7	33.8	26.7
Youngest.....	13.0	13.0	22.0	13.0
Oldest.....	65.0	49.0	67.0	49.0

All of our patients had pulmonary tuberculosis. Many entered the hospital with far advanced tuberculous disease which terminated fatally soon after admission. Seventy-nine per cent of the patients had pathological evidence of tuberculosis of the alimentary canal as well as evidence of tuberculosis of the accessory organs of digestion. In the remaining 21 per cent of cases careful gross and microscopic study failed to uncover evidence of gastro-intestinal tuberculosis.

The symptoms manifested by our group included general digestive disturbances, loss of appetite, nausea, vomiting, pain and discomfort in the abdomen, constipation, diarrhea and pain on swallowing.

**General Digestive Disturbances.**—Under this heading were grouped those patients with complaints which were vague and which Friedenwald and Morrison<sup>1</sup> have classified as dyspepsia. They embraced the following:

Distress after eating . . . . .	12
"Sour stomach" . . . . .	8
Acid eructations . . . . .	7
Heart burn . . . . .	1

In one case a diagnosis of gastric ulcer was made four years before the onset of pulmonary tuberculosis. The digestive symptoms referable to the ulcer were intensified by the intestinal tuberculosis. There was no evidence of tuberculosis of the stomach in this patient at autopsy. Tuberculous ulcer of the stomach is exceedingly rare. In Goldberg's<sup>2</sup> series, it occurs in 0.6 per cent of cases. In our studies there was no case of primary tuberculous ulcer of the stomach. In the case cited a few tubercle bacilli were found in the margin of the existing peptic ulcer.

**Appetite.**—While loss of appetite is not characteristic of gastro-intestinal tuberculosis 26 or 33 per cent of our cases noted a decided loss of appetite. Eight or 10 per cent of the patients noted that there was no alteration in their appetite and 4 or 5 per cent listed their appetites as fair. Friedenwald and Morrison<sup>1</sup> noted loss of appetite in 28 per cent and a normal appetite in 10 per cent of their cases.

**Nausea.**—Nausea is not an uncommon symptom and is often associated with loss of appetite and vomiting. It occurred at different times of the day and was not consistently related to meals. Brown and Sampson<sup>3</sup> reported an incidence of 52 cases in their series of 100 patients selected for study. Friedenwald and Morrison<sup>1</sup> noted that it occurred in 18 of their 50 patients. In our series nausea occurs in 18 or 25 per cent of the patients.

**Vomiting.**—This symptom occurs with or without nausea. Not infrequently vomiting follows a spell of coughing and occasionally follows meals. When at the latter time, the food is ejected in an undigested state. Fenwick<sup>4</sup> recorded the incidence of vomiting in 32 per cent of his series. Brown and Sampson<sup>3</sup> noted vomiting in 37 per cent of their cases. Erickson<sup>5</sup> noted vomiting in 37 per cent of his cases. In our series of 100 patients vomiting occurred in only 23 per cent. It occurred following coughing in 6 patients. In only one case was the vomiting listed as severe.

**Pain and Abdominal Discomfort.**—Abdominal pain is not a frequent complaint in the advanced stages of gastrointestinal tuberculosis. It may be referred to the epigastrium or right lower quadrant, and may be characterized as cramp-like or even colicky in nature. As a rule it is not severe pain but is usually referred to as "a soreness," deep, aching or vague in character. The timing of the pain was not accurate and occurred at variable times of the day and night, somewhat more frequently following meals as a "distress," but occasionally in the interval between meals. Engelsmann<sup>6</sup> noted pain in 22 per cent of his cases. Fenwick<sup>4</sup> recorded the incidence of pain as occurring in 41 per cent of his series, while Friedenwald and Morrison<sup>1</sup> noted an incidence of 86 per cent. Brown and Sampson<sup>3</sup> found that 7 per cent of their patients had no pain until late in the disease. In our series of cases 92 per cent complained of abdominal pain or some form of abdominal discomfort. Fifteen per cent of patients did not note abdominal discomfort until the terminal stage of the disease.

**Disturbance of the Bowels.**—Constipation of varying degree was noted in an appreciable number of cases. While constipation is common early in pulmonary tuberculosis occasional attacks of diarrhea may occur. Constipation may be followed by diarrhea or one may have alternating constipation and diarrhea as was noted by Burnand and Perret.<sup>7</sup> Lebert<sup>8</sup> was of the opinion that diarrhea without ulceration occurred in from one tenth to one seventh of all cases coming to necropsy. It is beyond the scope of the present discussion to attempt a description of the stools in intestinal tuberculosis. As a terminal event the diarrhea may be intractable and not infrequently resists any and all treatment. In itself, it may influence the course of the disease. Disturbed bowel function was noted in 28 per cent of our cases in the advanced stages of the disease.

Chart 2 indicates the incidence of general symptoms not referable to the gastro-intestinal tract in our series of cases. For purposes of future reference it is necessary to note the incidence in both sexes of the white and negro races separately.

CHART 2

CLINICAL SYMPTOMS (OTHER THAN GASTRO-INTESTINAL) IN PULMONARY TUBERCULOSIS

	<i>White.</i>		<i>Colored.</i>	
	<i>Male.</i>	<i>Female.</i>	<i>Male.</i>	<i>Female.</i>
Contact	6	5	0	4
Cough . .	21	21	12	14
Expectoration	11	15	8	9
Hemoptysis	9	9	4	3
Chills . .	7	1	1	1
Fever	14	7	3	8
Sweats	14	5	6	8
Dyspnea	7	3	2	3
Fatigue	22	18	6	12
Weakness	20	15	8	10
Loss of weight	17	17	11	9
Average loss of weight	4.6 lbs. per mo.	3 lbs. per mo.	4 lbs. per mo.	5 lbs. per mo.

**Physical Examination.**—Edwin Klebs,<sup>9</sup> in 1868, was the first to call attention to the fact that intestinal tuberculosis secondary to pulmonary tuberculosis was almost always due



to swallowing of the tubercle bacilli. Tubercle bacilli were present in the sputum of 85 per cent of our cases. Williams and Gardner<sup>10</sup> found pulmonary cavitation in 88 per cent of 169 cases. In our series, 41 patients or 52 per cent had a caseous-pneumonic form of tuberculosis according to the classification of Ornstein, Ulman and Dittler.<sup>11</sup> The incidence of positive sputum in our group was 73 per cent as against 27 per cent of the patients with cavitation who failed to show tubercle bacilli on repeated examination. The sputum ranged from Gaffky 3 to Gaffky 10 in the cases of caseous-pneumonic pulmonary tuberculosis. In the cases of chronic pulmonary tuberculosis without pathologically demonstrable cavities the Gaffky count was from 2 to 5.

**Temperature.**—The temperature chart of patients with secondary gastro-intestinal tuberculosis does not conform to any particular or characteristic pattern. It may be normal, low grade, or septic in type. In 30 of our patients (38 per cent), the temperature was characterized as septic; 43 of the patients (54 per cent), ran a low-grade fever, and in 27 patients (34 per cent), there was no elevation of temperature at any time during the course of the disease.

**Gastric Analysis.**—Hausman,<sup>12</sup> Bassler,<sup>13</sup> Gray and Ornstein,<sup>14</sup> Levy and Kantor,<sup>15</sup> Granet and Ornstein<sup>16</sup> have reported on the gastric findings in pulmonary tuberculosis. Gastric extraction was performed in 9 of our patients. Tubercle bacilli were found in the centrifuged sediment of 4 patients and were not found in the centrifuged sediment of 5 patients. All of the patients whose gastric contents contained tubercle bacilli were females. No attempt is made at this time to discuss the relationship of sex and duration of the tuberculous process to the gastric acidity. Gray and Melnick<sup>17</sup> have reported that tubercle bacilli in gastric washings are found more frequently in the female than in the male patients. This may be accounted for by the fact that the female because of her social habits may be less inclined to expectorate and swallows the sputum. These authors point out that the

presence of hydrochloric acid in the gastric secretions is a factor.

**Stool.**—The value of tubercle bacilli in the stool of patients with tuberculosis has been much disputed. Lichtheim,<sup>18</sup> Rittel-Willenke<sup>19</sup> and Gant<sup>20</sup> and others adhere to the school which contends that the isolation of tubercle bacilli from the stool constituted positive proof of the presence of intestinal tuberculosis. On the other hand, the work of many excellent investigators such as Biermann<sup>21</sup> and Klose<sup>22</sup> has shown that tubercle bacilli may be found in patients without evidence, even at postmortem, of intestinal tuberculosis. The presence of tubercle bacilli in the sputum is held as an important factor. The bacilli which are swallowed pass through the gastro-intestinal tract without producing any pathological changes. In our series 17 patients had stool examinations for tubercle bacilli. In 9 patients bacilli were found and in 8 patients no organisms were found.

**Abdomen.**—Abdominal examinations are of questionable value in establishing a diagnosis of a complicating gastro-intestinal tuberculosis. Careful examination may reveal some thickening of the cecum or a mass in the right lower quadrant. There may be pain or tenderness over the area of involved intestine. It should be borne in mind that marked tenderness and rigidity usually signify involvement of the peritoneal surface of the affected portion. In 84 per cent of our patients the abdomen was noted soft, distention was recorded in 11 per cent and tenderness was noted in 12 per cent. The abdomen was reported as doughy twice and there was moderate voluntary spasm three times. Ascites was noted in 3 patients. The liver was palpable and soft in 10 patients and the spleen was easily felt in 6 patients. On two occasions splenomegaly was noted without enlargement of the liver and on three occasions the liver was enlarged without evidence of splenomegaly. Fistula in ano was reported in 1 patient.

Chart 3 indicates the distribution of the lesions as found at postmortem.

## CHART 3

## PATHOLOGICAL FINDINGS IN ONE HUNDRED AUTOPSIES (79 PER CENT WITH GASTRO-INTESTINAL TUBERCULOSIS)

	<i>Number of cases.</i>	<i>Per cent.</i>	<i>Goldberg's percentage based on study of 179 cases.</i>
Tongue.....	2	2.5	0.6
Stomach.....	1	1.2	0.6
Duodenum.....	7	8.8	3.8
Jejunum.....	24	30.3	21.8
Ileum.....	62	78.4	83.2
Cecum.....	62	78.4	87.0
Appendix.....	21	26.5	39.1
Ascending colon.....	43	54.4	
Transverse colon.....	26	32.9	
Descending colon.....	17	21.5	
Rectum.....	6	7.5	

For purposes of comparison we have used the per cent incidence as noted by Goldberg.<sup>2</sup> We were unable to record the comparative statistics of the incidence of tuberculous involvement of the colon because in our series the colon was divided into three parts, the ascending, transverse and descending portions. The presence of ulceration was listed in each part individually. We therefore have overlapping and could not compare the incidence of tuberculous ulceration of the colon in our series with that reported by Goldberg.

## CHART 4

## PATHOLOGICAL FINDINGS (IN ONE HUNDRED AUTOPSIES—79 PER CENT WITH GASTRO-INTESTINAL TUBERCULOSIS) IN ACCESSORY DIGESTIVE ORGANS

	<i>Incidence.</i>	<i>Per cent.</i>
Mesenteric lymph nodes	39	49.3
Peritonitis.....	9	11.4
Liver.....	35	44.3
Gallbladder.....	1	1.2
Bile ducts.....	2	2.5
Spleen.....	38	48.1
Adrenals.....	4	5.0

In the one case of tuberculosis of the gallbladder there was associated tuberculosis of the gastro-intestinal tract. Jaundice was not present in either of the two cases of bile duct tuberculosis. In one of these there was associated tuber-

culosis of the gastro-intestinal tract. In the other tuberculosis of the bile duct was the only evidence of tuberculosis in the abdominal cavity.

**Comment.**—In view of the fact that 79 per cent of these patients had evidence of multiple lesions in the gastro-intestinal tract, it is difficult to correlate with any degree of certainty the relationship between the clinical symptoms and the pathological findings. Vomiting occurred in 23 per cent of the group, nausea in 25 per cent, general digestive disturbances in 28 per cent, bowel disturbances (constipation and diarrhea) in 28 per cent, loss of appetite in 33 per cent and varying degrees of abdominal pain and discomfort in 92 per cent. It is evident that practically all of the patients had some abdominal complaints. The intensity, duration and character of the abdominal symptoms are quite variable and bear no direct relationship to the pulmonary process and to the pathological lesions present in the gastro-intestinal tract. In this group of 100 patients with pulmonary tuberculosis, 79 per cent had pathological changes in the gastro-intestinal tract and 21 per cent had no demonstrable lesions, gross or microscopic, of tuberculosis.

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## CLINIC OF DR. POL N. CORYLLOS

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### A NEW CONCEPTION OF THE MECHANICS AND PHYSIOLOGY OF COUGH

(Action of Diaphragm in Cough)\*

COUGH reflex has become of major interest to the thoracic surgeon. Cough is at the same time a "watch-dog" of the bronchial tree, as Jackson named it, and one of the most powerful factors of dissemination of pulmonary infections. Its suppression during the immediate postoperative period favors the accumulation and retention into the bronchi of bronchial exudate, which is the main cause of hemorespiratory complications and of the dreaded syndrome of bronchial obstruction. On the other hand, as Ameuille, Archibald, Brown and, more recently, Balloon have shown, it promotes the spread of infected mucus into the small bronchi, and the production of "infectious bronchial embolisms," as named by Ameuille.

A number of fundamental problems related to the pathogenesis, and to the mechanics of cough are still unsolved. I shall only mention the uncertainty regarding the contribution of cough to the production of lesions such as spontaneous pneumothorax, of bronchiectasis, and the degree and nature of participation of the diaphragm in cough.

#### MECHANICS OF COUGH

I believe that a great deal of our discussions on cough are due to our rather confused actual conceptions of the mechanics

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of this complicated phenomenon. In fact, cough is neither a simple aspiratory act nor should it be considered as a whole. It is really composed of three distinct and different phases, which can be described as follows:

*First, the inspiratory phase.* A deep inspiratory movement in which the chest is dilated by the combined action of the intercostal muscles, the elevators of the ribs, the accessory inspiratory muscles, and the diaphragm. In this phase, the lung is "loaded" with air.

*Second, the compressive phase.* A short, sudden and powerful expiratory movement during which the *glottis is kept closed*. During this phase a considerable pressure is built up in the lung, which reaches and may exceed 100 mm. of mercury.

*Third, the expulsive phase.* While the expiratory movement is maintained the glottis is slightly opened, allowing the forceful expulsion of the previously compressed air. A strong draft of air is thus formed which causes the expulsion of foreign matter present in the bronchial tree and irritating the bronchial mucosa.

Thus cough is neither a pure inspiratory nor a pure expiratory act. It is a combination of both, aiming at the expulsion of foreign matter from the bronchi. As such it presents a peculiar likeness with the action of a gun. All three phases of cough are very clearly reproduced in the deflagration of a gun: the loading of the gun, the explosion of the powder and building up of pressure, and finally the expulsion of the bullet. Comparison with a compressed air gun is even more striking.

The importance of this division of cough into three phases becomes readily apparent when we study the physiological characteristics of each.

**The Inspiratory Phase.**—During the inspiratory phase, the chest dilates and the diaphragm contracts and moves downward. Therefore, the intrapleural pressures become strongly negative. It should be pointed out, however, that this increase in the negative value of the intrapleural pressures is equal in both pleural cavities only if the two lungs are healthy, or dis-

cause in dealing with cough we seldom deal with perfectly normal lungs, and it would be fundamentally wrong to forget the pathologic physiology of the diseased lung.

When the chest dilates, the lung is forced to expand, air rushes into it, the lung inflates and this inflation neutralizes a part of the negative intrapleural pressure by filling the enlarged chest cavity. But the rapidity and completeness with which the expansion of the lung takes place depends upon several factors. The first is that of patency of the upper respiratory ways—larynx, trachea and large bronchi. When, for example an obstacle is present in a common bronchus, the corresponding lung cannot expand, the increased capacity of the chest cannot be filled, and consequently the intrapleural pressure in that hemithorax presents a very considerable decrease, that is, it becomes more negative than in the healthy side. Another cause leading to the same effect is consolidation of the lung. Again, the lack of expansion of the lung, or increased resistance to its expansion, will cause a greater negative pressure during inspiratory enlargement of the chest. After all, it should not be forgotten that negative intrapleural pressure is due to and measures the elastic recoil of the corresponding lung. The results of this abnormal increase of the negative value of intrapleural pressure are numerous. First, in a tuberculous lung, it may facilitate the perforation of superficial subpleural pulmonary caseated areas and, consequently, the production of spontaneous pneumothorax. Therefore, it is a therapeutic necessity to moderate cough in advanced cases of pulmonary tuberculosis. This is even more imperative following intrapleural pneumonolysis, especially when extensive dissections of the adherent lungs were carried out, particularly in cases with bilateral pulmonary tuberculosis.

A corollary of bronchial stenosis, of bronchiolar and alveolar atelectatic consolidation or even of paralysis of the diaphragm is the considerable decrease of the amount of air which can be loaded during this phase into the lung behind foreign matter present in the bronchi. Thus, during the compressive phase very little compression can be built behind the



foreign bodies to be expelled. Hence little or no expulsion will take place in the expulsive phase. A bullet cannot be propelled through the barrel of a gun unless gun powder explodes behind it. Another corollary of the high negative pressure developed in the diseased side during the inspiratory phase is the deviation of the mediastinum. When the contralateral lung is healthy and can expand readily, the intrapleural pressure in that side is obviously less negative than in the side of the diseased lung which cannot expand. Therefore, the mediastinum is deviated toward the side of the latter with a maximum of bulging—mediastinal hernia—at the end of inspiration. The heart is likewise displaced toward the diseased side, causing, occasionally, torsion of the large vessels with distressing symptoms.

Finally, lack of expansion of the diseased lung restricts the inspiratory enlargement of the corresponding hemithorax, thus diminishing the efficiency of this first phase of cough, or even causing inspiratory retraction of the chest wall, known as paradoxical respiration.

**The Compressive Phase.**—During the second phase of cough the mechanical and physiological phenomena differ entirely. Sudden contraction of the expiratory muscles, the most important of which are the abdominal muscles, materially decreases the chest capacity. The glottis being closed the lung is greatly compressed, and the intrapleural and intrapulmonary pressures become highly and equally positives: 80 to more than 100 mm. of mercury. Since the alveoli are more compressible than the bronchioli and the bronchi, the latter remain patent because of the pressure exerted into them by the compressed alveolar air. The rupture of caseated spots of the lung or of blebs is, theoretically at least, least likely to occur during the second phase. It is difficult to conceive how even a thin bleb can burst if the pressures exerted upon the two surfaces of its walls are equal. During the compressive phase, because of the closure of the glottis, the pressures are independent of the condition of the lung. They are equal in both lungs not only because of their intercommunication, but also

because of the mechanical conditions under which the pressure into and outside of the lungs is built. Authors who consider cough as a whole surmise that it is represented by this compressive phase alone. Thus, Hedblom refused to admit that cough plays any part in dilatation of the bronchi in bronchiectasis. He said, "During cough pressure is uniformly increased inside and outside of the lung so that no dilatation of the

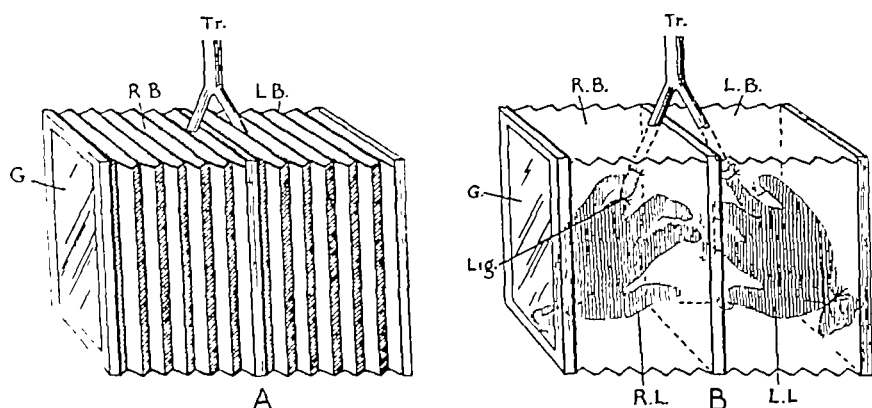


Fig. 73.—Artificial chest. The keyboards of an accordion were removed and replaced with plate glass (A, G) air-tightly fixed in place. In the middle of the accordion a partition was built (B) composed of a wooden frame covered with a thin elastic sheath of dental rubber. The two legs of a Y glass tube (Tr.) were passed through the upper wall of the accordion on each side of the partition. To each of these branches a rubber glove, the cuff of which was tightly ligated, was affixed by means of a hole that had been made in the tip of the ring finger (A and B, R.L., L.L.). In this device the accordion represents the chest, the capacity of which could be made to increase or decrease by opening or closing the accordion, the elastic partition represents the mediastinum, the gloves take the place of the lungs; the Y tubes portray the trachea and common bronchi. An incomplete ligature was placed in the ring finger of one of the gloves (B, lig.) representing a stenosis of the bronchus

bronchi can occur, however diseased and softened their walls may be." This statement, although correct when applied to the compressive phase of cough alone, is entirely wrong when pertaining to cough in general.

**The Expulsive Phase.**—The third phase of cough is the most important. To study it minutely, an artificial chest was constructed in my laboratory using an accordion (Fig. 73).

The keyboards were removed and replaced with plate glass, airtightly fixed in place of the keyboards. Then, in the middle of the accordion, a partition was built, composed of a wooden frame covered with a thin elastic sheath of dental rubber. After this, two legs of a Y glass tube, were passed through the upper walls of the accordion, on each side of the partition, and to each a rubber glove, the cuff of which was tightly closed, was affixed by means of a hole that had been made in the tip of the ring finger of the glove. When completed, the device consisted of an accordion representing the chest, the capacity of which could be made to increase or decrease by opening or closing the accordion, an elastic partition representing the mediastinum and a pair of gloves taking the place of the lungs, with the Y tube portraying the common bronchi in its two horizontal branches and the trachea in its vertical branch.

Let us watch, now, the successive phenomena in the expulsive phase of cough, which begins with the opening of the glottis. The air compressed in the lungs rushes out as a strong and sonorous draught, carrying with it foreign matter lodged in the bronchi; intrapulmonary pressure rapidly drops until it equals the atmospheric pressure and expulsion then ceases.

There is no difficulty in understanding the mechanics of this phase when the lungs are healthy and the diaphragm normal. It is different when the lung is diseased or the diaphragm paralyzed.

Let us see what happens in the instance of a lung with collapsed alveoli, and retention of exudate in the corresponding bronchi. Stasis and impaired bronchial drainage mean infection of the bronchi with aerobic organisms in the beginning, and anaerobic later, as the oxygen contained in the exudate is absorbed by the white cells and the aerobes. This combined infection leads to the injury and gradual destruction of the musculo-elastic element of the bronchial walls, and to their replacement by connective tissue. With destruction of the elastic and muscular elements, the tonus of the bronchial walls

decreases and so slight and cylindrical dilatation of the bronchi at the diseased portions is produced. However, the nearby bronchi which are still adequately drained and healthy are narrower than the diseased peripheral bronchi, because of: (1) the integrity of their elasticity and tonus, and (2) their reflex contraction due to irritation exerted on their mucosa by the inflammatory process in their neighborhood. The demarcation between the diseased and healthy areas is sharply made and it appears as a stricture. The descriptions of these changes in the bronchiectatic lung by Cruveilhier (1856), Charcot (1881), Marfan (1901), and by other pathologists are classic.

During the first, or inspiratory, phase of cough, the healthy and diseased bronchi are filled with air as a result of the length of this phase and the inspiratory expansion of the bronchial tree. During the second, or compressive phase nothing happens for, as explained above, the pressures inside and outside of the bronchi are equal; but, during the third, or expulsive, phase of cough the mechanism of egress of air from the healthy and from the diseased bronchi are radically different. In fact, air rushes out of the healthy bronchi easily, since their diameter increases toward the lobar bronchus and there is, therefore, little resistance to the expelled air, the pressure falling very rapidly to the level of atmospheric pressure. In the diseased areas, on the contrary, the narrowings above the enlarged bronchi offer a considerable resistance to the egress of air. Thus, at the time that the pressure in the healthy parts of the lung has already reached the atmospheric level, it is still above that level in the diseased bronchi. In other words, during the expulsive phase of cough pressures are higher into the diseased than in the healthy bronchi. Obviously this difference of pressures must cause a gradual and progressive dilatation of the diseased bronchi. This is not theorizing because it is by the same well-known mechanism that obstructive emphysema is produced. In bronchiectasis, instead of dilatation of the alveoli as in emphysema, dilatation of the bronchi takes place; in fact, when the alveoli have undergone inflammatory

organization and definite closure following plastic alveolitis or pulmonary sclerosis or organized atelectasis, which can be caused by any pulmonary lesion, chronic retention of bronchial exudate is established in the bronchi. Bronchial stasis takes place in these test tube-like bronchi because the absence of air distally brings about suppression of the expulsive phase of cough which represents the most efficient mechanism of bronchial drainage.

This is not all, however.

Owing to the narrowing of the bronchial lumina above the diseased bronchi, the air is not completely expelled at the end of the expulsive phase of cough. Thus, the beginning of the next inspiration finds the diseased areas still air-containing so that the discrepancy in pressure during the expulsive phase between healthy and diseased bronchi is still further increased. This mechanism of production of bronchial dilatation or obstructive emphysema was clearly demonstrated with the artificial chest. When an incomplete ligature was placed on the finger connecting one of the gloves to the Y tube (Fig. 73, B, lig.) to produce narrowing of the finger, it was found that after opening and closing the accordion in imitation of a number of strong inspiratory and expiratory movements, if the motion was halted in expiration the glove representing the diseased lung remained expanded, due to the narrowing of the finger, whereas the other glove collapsed. This has furnished additional proof in support of my contention that, contrary to prevailing opinion, bronchial dilatation in bronchiectasis is due to cough.

#### ACTION OF THE DIAPHRAGM IN COUGH

The function of this musculo-aponeurotic membrane in cough has acquired considerable importance since the widespread practice of phrenic nerve interruption in the treatment of pulmonary tuberculosis. In reviewing the literature, we find the most contradictory statements. Many sponsors of paralysis of the diaphragm in the surgical treatment of pulmonary tuberculosis claim that by this method "expectoration is increased and rendered easier." Others, however,

maintain that expectoration decreases and that diaphragmatic paralysis favors the development of bronchial retention and obstruction. Still another group report no sizable changes. What are the real results of interruption of the phrènic nerve? What is the rôle of the diaphragm in the phenomenon of cough?

*A priori*, there should be none. The diaphragm being an exclusively inspiratory muscle should have nothing to do with cough, if cough is regarded solely as an expiratory phenomenon. The inability of physiologists and clinicians to offer a definite solution to this problem was evidenced in an editorial on cough in the J.A.M.A. in 1928 (xci, 1894) in which there appeared this statement: "In all acts of expulsion, sneezing, coughing, laughing, vomiting, and crying, the diaphragm adds force to the expulsion efforts." Surprised by this statement, Dr. W. D. Toethout addressed a letter to the editor (xcii, 496, 1929) as follows: "Kindly explain how the contraction of the diaphragm can contribute to expiratory efforts." The editor (xcii, 496) in his answer corrected his previous statement and acknowledged: "There is at present no evidence that the diaphragm adds power to these processes (sneezing, coughing, laughing and crying which are expiratory acts) and of favoring the expulsion of air from the lungs."

Should we then conclude that the diaphragm is of no importance in the act of cough?

Certainly no one will deny that contraction of the diaphragm produces a powerful compression of the abdominal viscera; thus, when the diaphragm and the abdominal muscles contract simultaneously the diaphragm concurs to the increase of intra-abdominal pressure and to the expulsion of the contents of the abdominal viscera either through the mouth (retching, vomiting), or through the rectum (defecation), or through the urethra (urination). In these phenomena, however, it is to be noted that the diaphragm acts as an abdominal and not as a thoracic muscle. Its action is two-fold: direct, *i. e.*, pressure upon the viscera. and indirect, *i. c.*, immobilization of the chest upon inspiration with a closed glottis, so that there is

furnished a solid, unyielding upper insertion to the abdominal muscles, especially to the recti and the obliques.

But when the diaphragm is functioning as a thoracic muscle, its action is totally different.

During the *inspiratory phase* of cough, or of laughing, sneezing, crying, or singing, the participation of the diaphragm is obvious; it is an essential factor in loading the lungs with air. When it is paralyzed, there is less marked inspiratory enlargement of the corresponding hemithorax and lung and less than normal amounts of air are drawn into the lung; the immobility or even the rise of the paralyzed diaphragm during inspiration does not produce the necessary increase of the vertical diameter of the hemithorax. This deficiency is more marked in patients with thoracoplasty in which costal motion is suppressed.

It is my contention that the action of the diaphragm is equally important during the second, or *compressive phase* of cough. It is obvious that positive pressure in the chest cannot be produced unless its walls have become rigid and unyielding. Immobilization of the ribs by the contraction of the expiratory muscles insures such rigidity. But since the floor of the chest cavity is represented by the diaphragm, so long as this part of the chest is not rigid no high positive pressure can be attained in the chest. This can only be accomplished by the simultaneous contraction of the diaphragm and of the abdominal muscles.\* Only by the push of the abdominal viscera against the contracted diaphragm can this rigidity of the floor of the chest be insured. Therefore, we must conclude that in the compressive phase of cough the diaphragm acts as an antagonist to the abdominal muscles; and, since the principal expiratory muscles are the abdominal muscles, we must admit that, apparently at least, *not only the diaphragm does not help cough, but, on the contrary, it opposes it by restraining the elevation of the abdominal viscera*. It seems, therefore, that the

\* It may be a matter of discussion whether a real contraction of the diaphragm takes place or the tonus (or status) of this musculo-aponeurotic membrane suffices to insure the rigidity of the floor of the chest. This question will be taken up in a forthcoming paper.

*expulsive action of cough is under the control of two antagonistic muscular systems: of the diaphragm and the abdominal muscles.* So far as I know, this concept of the action of the diaphragm has not been presented hitherto. It is, however, of great significance because, if I am right, it explains the mechanism of the refined regulation of the expulsive action of cough. In fact, all movements in the organism, skeletal or visceral, are dependent upon two antagonistic muscular systems. By means of the fine interplay of these antagonistic systems acting synergistically, with one acting as a brake upon the other, movements are regulated to a smooth course with a minimum loss of time and energy and a maximum of accuracy.

In the third, or *expulsive*, phase of cough, this action becomes more apparent. If we inspect the abdomen of a man during cough, we see that in each coughing effort a movement of retraction of the abdominal wall takes place. When a subject is instructed to perform successive movements of cough without inspiratory interruption, we see successive contractions of the abdominal wall so that it retracts each time a little more than in the preceding movement. When the subject is examined fluoroscopically under the same conditions, the diaphragm is seen to assume a more elevated position with each cough. It does not permit the abdominal viscera to jump upwards into the chest cavity as occurs when the diaphragm is paralyzed; the intact diaphragm opposes, limits and regulates the visceral push. This is particularly noticeable when a subject makes successive movements of cough in an endeavor to expel tenacious sputum; in each movement of the cough the diaphragm rises a little more, thus preventing the waste of air enclosed in the lungs and making the best use of it. In other words, the synergic action of these two antagonistic muscular systems regulates the action of cough and adjusts its expulsive strength to the resistance offered by foreign bodies lodged in the bronchi.

*I believe, in short, that it is unwarranted to accept that the diaphragm "helps cough" or "opposes it" or "has nothing to do with cough." The rôle of the diaphragm in cough is a*



*different one. It is a "coordinator of cough," insuring the fine adjustments of cough by regulating its action and strength to the resistance to be overcome.*

#### EXPERIMENTAL DATA

Experimental and clinical studies of animals and patients with a paralyzed diaphragm have corroborated this conclusion.

Experimental investigations upon changes in cough after phrenicectomy in dogs have recently been carried out by Carlsen, Balloon, Wilson and Graham, Kinsella, and more recently by Fine and Starr. Graham and his collaborators found that the efficiency of cough is decreased after phrenicectomy, as shown by retarded elimination of lipiodol in the side of the paralyzed diaphragm. Kinsella has found this to be true, also, in the human. Fine and Starr conceived the idea of performing bilateral phrenicectomy on dogs in order to eliminate any possible error due to contraction of the contralateral diaphragm. After graphs were taken by these authors on the normal animal, both phrenic nerves were cut by pulling on wires that had been previously placed around them. No change in the height of the expiratory blasts could be noted and so Fine and Starr concluded that "paralysis of the diaphragm affords neither help nor hindrance to the force of the expiratory blast. . . . If cough is somewhat less efficient it must be related to other factors such as reduced expansion of the lungs with consequent decrease in the air available for the expiratory blast."

These experiments, however, convey only a rough idea of what happens in cough. They register the final results of phrenicectomy upon the strength of the expiratory blasts, but do not furnish information regarding the finer changes of intrapleural and intrapulmonary pressures during the different phases of cough in patients with or without a paralyzed diaphragm.

Therefore, we have deemed it of interest to conduct a number of experiments upon patients with a pneumothorax and having an intact or a paralyzed diaphragm.

We conjectured that, since changes of intrapulmonary pres-

sure are due to, and caused by, changes in the capacity of the chest cavity, measurement of intrapleural pressures might supply accurate information as to what happens during cough. On the other hand, recording the changes of intrapleural pressures during cough in the human would eliminate a number of errors likely to occur in experiments on animals, especially the dog. In fact, in animals the cough should be produced by artificial stimulation after anesthetizing the animal; in the dog the flexible mediastinum cannot be likened to the more resistant human mediastinum.

Two of the patients in whom the experiment was carried out had the following histories:

**Case I.**—T. G., twenty-three, female Puerto Rican, bilateral pulmonary tuberculosis: had had bilateral pneumothorax, completed by bilateral pneumonolysis. Both upper lobes were selectively collapsed while the lower lobes of both lungs were allowed to reexpand. The vital capacity was 1200 cc. The phrenic nerves were intact and the function of the diaphragm was normal. Ambulatory case.

**Case II.**—F. L., twenty-two, female, white, had a pneumothorax in one side. A complete avulsion of the phrenic nerve (30 cm.) had been performed previously. Pneumonolysis was performed for section of apical adhesions which had opposed a selective collapse of the apex. Actually the upper lobe was selectively collapsed while the lower lobe was allowed to reexpand. Vital capacity 1400 cc. Ambulatory case.

The two cases were as similar as could be, with one exception: the diaphragm of Case II was paralyzed.

**Technic.**—A needle was introduced into the pleural cavity of each patient and tracings were taken by means of a chloroform recording manometer on a revolving smoked drum. In Case II, the needle was introduced into the side corresponding to the paralyzed diaphragm.

The patients were instructed to cough twice in succession and without inspiratory interruption so that each curve on the graph would represent two movements of cough without an intervening inspiration.

The tracing of Case I (normal diaphragm) is represented in Fig. 74. A few quiet respiratory movements were recorded (inspiration appearing in downstrokes) before the subject

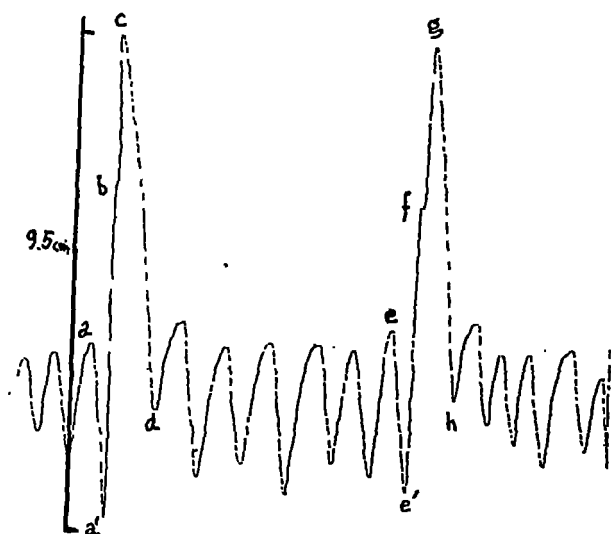


Fig. 74.—Graph of cough of a patient with pneumothorax and normal diaphragm. See details in the text

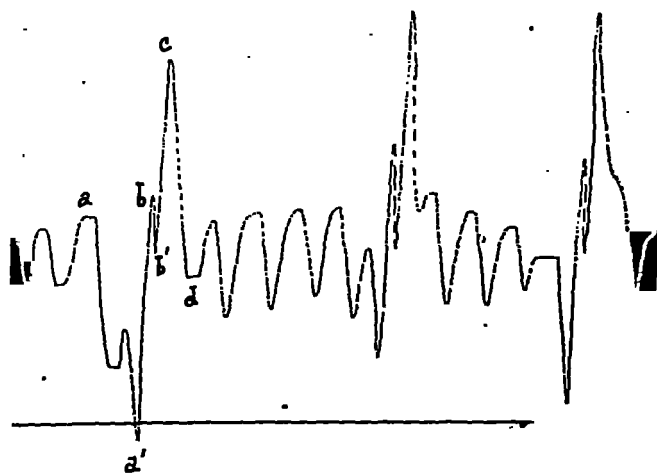


Fig. 75.—Graph of cough of a patient with pneumothorax and paralyzed diaphragm by previous phrenicectomy. See details in the text

coughed. Analyzing the graph,  $a-a'$  represents the deep inspiration preceding cough (inspiratory phase);  $a'-b$ , the compressive and expulsive phases of the first cough;  $b-c$  the same phases of the second cough; and  $e-e'$  and  $e'-f-g-h$  repetitions of the same movements.

In Fig. 75 the record of Case II is shown.  $a-a'$  again represents the inspiration preceding cough;  $a'-b$  the first cough; and  $b'-c$  the second cough. The remaining two tracings repeat the phenomenon.

In both tracings,  $a-a'$  represents the first inspiratory phase;  $a'-b$  and  $b-c$  the second, or compressive phase, and  $c-d$  the end of the expulsive phase. All other conditions being alike in both cases, it is reasonable to conclude that whatever the differences, if any, in the two tracings, they must be attributable to the paralysis of the diaphragm in Case II.

In Case I the inspiratory phase is represented by a clean-cut vertical line,  $a-a'$ . In Case II this line  $a-a'$  is interrupted and less vertical. Obviously, therefore, inspiration was less efficient in Case II due to paralysis of the diaphragm.

In the second phase of cough, there are more interesting variations in the two tracings. In Fig. 74 a continuous effort is apparent, the expiratory strength being maintained throughout the duration of the two cough movements. Although there is a slight arrest in  $b$  and  $f$ , indicating the end of the first cough and the commencement of the second, there is no drop in pressure. In Fig. 75, however, we find that a marked drop in the intrapleural pressure occurred between the two coughs, represented by line  $b-b'$ .

Interpreting these experimental data, we find that in Case I, with an intact diaphragm, the upward push of the abdominal viscera, caused by the contraction of the abdominal muscles, was checked by the contracting diaphragm so that, between the first and second acts of cough, there was no drop in intrapleural pressure and none, consequently, in intrapulmonary pressure. Line  $b-c$  represents a continuation of line  $a'-b$ ; as does  $t-g$  of  $e'-f$ . On the contrary in Case II with a paralyzed diaphragm, the intrapleural, and consequently the intrapul-

monary pressures, dropped between the first ( $a'-b$ ) and the second ( $b'-c'$ ) movements of cough, due, I believe, to an absence of contraction of the diaphragm which permitted the abdominal viscera to jump upward unchecked, obedient to their inertia. When the push of the abdominal muscles was slightly and momentarily relaxed between the first ( $a'-b'$ ) and second coughs ( $b'-c$ ), the viscera, obedient to gravity, fell back ( $b-b'$ ), indicating a loss of energy. The result of this waste is shown in the decrease of the total height of the line  $a'-b-c$  of Fig. 75 compared to the height of the same line,  $a'-b-c$ , of Fig. 74. This waste of energy is even more considerable than is apparent in view of the fact that Case II had a greater vital capacity than Case I. Obviously, then, the diaphragm (an inspiratory muscle), by its cooperation with the abdominal muscles (expiratory muscles) in the regulation cough, the prevention of a waste of energy and the adjustment of its strength to the need, represents a vital factor in the efficiency of cough.

#### SUMMARY

Four new concepts are offered:

1. Cough is shown to be a complex phenomenon having three well-defined phases: inspiratory, compressive and expulsive. The mechanics and physiology of each phase are described.
2. The action of cough in the production of bronchiectasis is presented.
3. The action of the diaphragm in cough is studied. Clinical and experimental evidence is presented leading to a new conception of its action.
4. The diaphragm does neither help nor hinder the action of cough. It acts as a regulator of cough and adjusts its action to the resistance offered by foreign bodies lodged in the bronchi.

## CLINIC OF DR. MILTON A. BRIDGES

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#### DIET PRESCRIPTION FOR THE TUBERCULOUS\*

DIET plays an important rôle in both pulmonary and extrapulmonary tuberculosis. Irrespective of the psychologic import of gained weight with its euphoric acceptance by both the patient and the physician, a better understanding of the nutritional demands of the tuberculous does not always sanction this physical gain.

At this writing, pulmonary tuberculosis is evaluated, not by the extent of the disease, but by the character of the infection. The acute exudative forms present a sudden and toxic beginning. When this is associated with pulmonary necrosis, caseation and liquefaction promptly follow. The necrotic tissue is expectorated with resultant cavity formation. From the start of this type of tuberculosis, the victim is prone to be intensely toxic. With the expectoration of necrotic lung tissue, the symptoms of toxemia begin to disappear. Unfortunately, the resultant cavitation being an excellent culture medium for the tubercle bacilli, the bacteria multiply rapidly. This commonly results in further pulmonary involvement with recurrent toxemia.

Hence, the clinical picture of pulmonary tuberculosis is a variegated one as can be readily seen, requiring frequent dietary changes. Most difficulties are encountered during the febrile periods.

The dietetic care of febrile conditions has been universally divided into two types, one for fevers of short duration, such

\* The food listings and menus in this article have been taken from Bridges' "Dietetics for the Clinician," Lea & Febiger, Philadelphia, Pa.

as are encountered in influenza, la grippe, tonsillitis, etc. In these conditions the diet proves to be essentially one of starvation. Solid foods are prohibited and a high fluid intake with moderate carbohydrates, no fats and low in caloric value is instituted. This temporary starvation unassociated with acidosis proves beneficial and is felt to hasten convalescence.

The second type of dietetic care of the pyretic is directed at fevers of longer duration in which category tuberculosis probably is the most common.

Great credit should be extended to Coleman and Shaffer, who in 1907 presented to the medical profession a revolutionary diet for typhoid fever. Prior to their presentation the dietetic care of the typhoid was one of pseudostarvation for the duration of the disease, with the result that very commonly the period of convalescence exceeded by far, the time occupied by the acute course of the malady. The older interdiction of food was due to the always present fear of producing perforation or hemorrhage. As a result of this negative diet convalescence was occupied in restoring to normal, a markedly underweight, starved and anemic individual.

In the absence of knowledge of liver therapy, vitamins and the proper administration of hematics, as was the case several decades ago, it can be readily understood that the time consumed in accomplishing this desired restoration was tedious and often fruitless.

Those interested in nutrition have definitely reached the conclusion that poundage is not the *sine qua non* of health. The older school emphasized the continued gain of weight of the tuberculous patient. This they accomplished by what is now evident to be a shotgun overfeeding. Those whose work has been restricted to tuberculosis have seen the falsity of this trend of thought.

At the present writing, it has as yet been undetermined what rôle diet plays in establishing the resistance of the individual to tuberculosis. It is well recognized, however, that undernourishment predisposes to a questionable prognosis. Clinical experience has taught that a moderately high caloric

diet, well-balanced in minerals and vitamins offers a patient a more favorable outlook.

A review of the literature in reference to man's energetic requirements reveals many discrepancies. These variations in opinion are due to the inconsistency of recognition on the part of various observers, of the many factors which influence such requirements.

Age, sex, weight, height, size (surface area), muscular activity, body temperature, brain activity, together with climatic and other environmental conditions so alter requirements that it can readily be seen that no one formula can be applied to the feeding of the human mechanism in health or disease.

In spite of the presence of all these variables, some standard must be established in order to intelligently feed the sick. The consensus of opinion as to food requirements expressed in the amounts of carbohydrates, proteins and fats required by the average person (150 pounds) per diem, is: carbohydrates, 350 Gm.; proteins, 100 Gm., and fats, 150 Gm., totaling about 3200 Calories. This energetic requirement is estimated as being necessary for the average working man. Each of these components has been the subject of much divergence of opinion.

Recently an analysis of large groups of non-dieting individuals in a cosmopolitan city, revealed that the total protein intake per diem was closer to 50 than to 100 Gm. In urban life, the ingestion of 150 Gm. of fats seems reasonable. The inclusion of 350 Gm. of carbohydrates in the daily dietary of the average individual is subject to marked variation, due principally to occupational pursuits.

It is generally believed that the adult requires from 10 to 35 Calories per pound of body weight in direct relationship to an activity varying from resting to heavy physical exertion. In gross Calories calculated on the basis of 150 pounds, this means 1500 to 5200 Calories daily.

It has been well established that the presence of fever increases the body metabolism to an extent which requires greater caloric intake to offset the burning of endogenous nu-



tritive material. Hence, the total caloric intake demands an increase over the normal calculated maintenance level when fever is present. This is especially true in relation to the protein allotment.

The average daily mineral requirement is also subject to much controversy which in turn is based upon the question of availability and assimilation of the various minerals. The accepted guide for the daily requirement is considered to be: calcium, 10 mg.; phosphorus, 15 mg.; iron, 0.2 mg.; and magnesium, 0.3 mg.; per kilogram of body weight. A well-balanced diet fully meets these demands.

Coincident with the marked advances in physiology, biochemistry as well as mineral chemistry, feeding of the sick has departed markedly from the old axiom of just "feeding" to "prescription feeding." The author feels that the great amount of research which has been devoted to the study of diabetes and its associated problems has done more to enlighten the profession in reference to feeding of the physical being in both sickness and health, than any other factor in the study of disease. Recently, advances made in the dietetic care of gallbladder diseases again reveal a better understanding and evaluation of the relationships of food chemistry and physiology in conjunction with a newer understanding of the pathologic entities in the gastro-intestinal tract. As a result, the prescription of a diet for diabetes or the diseased gallbladder is no longer a ready-made coat to cover anybody, but a well-tailored garment fitted to the individual figure.

The proper approach to the dietetic care of the tuberculous patient is to initially establish a complete inventory of the physical being for whom a diet is to be prescribed. This comprises a complete chemical blood study with particular reference to blood calcium, urea nitrogen, nonprotein nitrogen, sugar, uric acid, chlorides, phosphorus and hemoglobin. An estimation of the presenting weight in relation to the calculated weight establishes an objective which should not be lost sight of.

Additionally, in order to avoid unpalatability and food aversion, cognizance must be taken of the past dietary habits and any existing intolerance or allergic reaction determined.

Another factor so often overlooked, is the lack of regard for the commonly associated anorexia. When the appetite is small it is ridiculous to outline large volumetric meals. This obstacle can frequently be met most simply by omitting all non-caloric bearing liquids, hence reducing the meals to items with high caloric yield.

It has generally been accepted that an overabundance of vitamins B, C and D are indicated. For ready reference the appended listing presents in concrete form the latest classification under these respective vitamins:

Vitamin B <sub>1</sub>	Vitamin C	Vitamin D
Dried brewer's yeast*	Citrus fruits*	Fish liver oils*
Wheat germ*	Parsley*	
	Peppers, green or red*	Burbot (European)
Avocado	Raw new cabbage*	Butter (variable)
Bread, whole wheat	Tomato juice*	Clams
Cabbage, raw	Watercress*	Cream
Carrots		Egg yolk
Fruits in general	Cranberries	Haddock
Leafy vegetables	Cucumbers	Halibut
Legumes	Fresh fruits	Herring
Nuts	Fresh, raw vegetables	Oysters
Okra	Pimentos	Salmon
Oysters	Potatoes	Sardines
Peppers	Tomatoes	
Pork		
Rice, brown		
Spinach		
Tomatoes		
Wheat bran		
Whole cereal grains		

The question of calcium administration should be based upon the blood calcium determination. However, the administration of foods high in calcium whether indicated by blood analyses or not has never been proved detrimental. The fol-

\* Outstanding

Following list presents a classing of foods which have been determined as containing the higher amounts of calcium:

#### FOODS HIGHEST IN CALCIUM

In order of decreasing percentage.

Skim milk powder	Kale	Wheat bran
Cheese, rennet	Caviar	Citron
Whole milk powder	Figs, dried	Cocoa, dry
Mustard	Navy beans, dried	Clams
Jelatin, dry	Watercress	Oats, entire
Turnip greens	Ice cream	Maple syrup
Malted milk	Whitefish	Cabbage greens
Condensed milk	Kidney beans, dried	Buttermilk
Filberts	Egg yolk	Endive
Evaporated milk	Boston brown bread	Lentils, dried
Molasses	Broccoli	Horseradish
Almonds	Cauliflower	Olives
Collards	Capers	Shrimp
	Whole and skim milk	

Even though phosphorus metabolism is intimately associated with that of calcium it might be well to list those foods highest in phosphorus:

#### FOODS HIGHEST IN PHOSPHORUS

In order of decreasing percentage.\*

Wheat bran	Oatmeal	Corned beef
Meat peptone	Chocolate, sweet	Brown rice
Wheat germ	Peas, dried	Rye flour
Skim milk powder	Barley, entire	Veal roast
Swiss cheese	Peanuts	Codfish, salt
Mustard	Rye, entire	Tuna fish, canned
Cocoa, dry	Lentils, dried	Salmon, smoked
Cheddar cheese	Beef brain	Mackerel
Whole milk powder	Corn, dried	Quail
Egg yolk	Wheat, entire	Chicken, lean
Tea	Turkey, light meat	Ham, fresh, lean
Navy beans, dried	Walnuts, English	Sardines
Cashew nuts	Filberts	Malted milk
Kidney beans, dried	Breakfast wheat	Whitefish
Almonds	Lima beans, dried	Cottage cheese
Chocolate, bitter	Pecans	Salmon, canned
Turkey, dark meat	Pot cheese	Whole wheat bread
	Beef, dried	

\* These items contain over 250 mg. per cent.

Subnormal blood nitrogen readings are pathognomonic of insufficient protein ingestion. Aside from the chemical blood findings the presence of fever always necessitates a higher protein intake than normal. For convenience appended is a list of those foods highest in proteins:

## FOODS HIGHEST IN PROTEINS

Almonds	Fish	Pine nuts
Butternuts	Fish roe	Pistachio nuts
Cashew nuts	Gelatin, dry	Poultry
Cheese	Gluten products	Protein milk
Crustaceans	Legumes, dried	Soy bean products
Eels	Meats, lean	Walnuts, black
Egg	Milk powders	Wheat cereals
	Peanuts	

In the presence of anemia, either nutritional or due to hemorrhage, it is indicated to administer those foods most capable of increasing hemoglobin. Fortunately, the dietetic care of pernicious anemia has resolved the blood-building chaos into a specific dietary prescription. The necessity of sufficient vitamin A in the correction of anemia has been widely stressed. A predominance of this vitamin is found in the following foods: butter, fish liver oils, tomato, egg yolk, milk and leafy vegetables, principally cabbage, cauliflower, lettuce and spinach. The effect of the ingestion of iron, as obtained from foods, is thought to be synergistically enhanced by the associated presence of copper and manganese. The following foods carry the highest combination of these three minerals:

Almonds	Cocoa, dry	Pineapple
Beans, kidney	Filberts	Pistachio nuts
Beans, lima	Lentils	Spinach
Beef juice	Liver, calves'	Walnuts
Cherries, fresh	Olives, green	Watercress
Chocolate, dry	Parsley	Wheat bran

Those foods containing the highest amount of iron, irrespective of their manganese or copper content, are herewith presented:

## FOODS HIGHEST IN IRON

In order of decreasing percentage.\*

Blood	Walnuts, black	Quail
Beef juice	Beef kidney	Chicken, lean
Parsley	Calves' liver	Oatmeal
Apple butter	Dates	Corn
Wheat bran	Beef heart	Veal roast
Beef liver	Currants, dried	Barley, cooked
Molasses	Breakfast wheat	Turnip greens
Pistachio nuts	Filberts	Sauerkraut
Egg yolk	Seedless raisins	Oysters
Sweetbreads	Chestnuts	Mushrooms
Watercress	Lean beef	Squab
Seeded raisins	Almonds	Mince meat
Butternuts	Spinach	Chocolate, bitter
Apricots, dry	Figs, dry	Cocoa, dry
Avocado	Brazil nuts	Maple syrup
Dried beef	Pickles, sweet	Bacon, crisp
Dandelion greens	Prunes, dried	Boston brown bread

The following foods have been proved to be highest in *hematopoietic power*:

Apples	Bone marrow	Lettuce
Apricots	Brains	Peaches
Asparagus	Calves' liver	Pig kidney
Beef heart	Chicken gizzard	Pineapple
Beef kidney	Chicken liver	Prunes
Beef liver	Fish liver	Raisins
Beef spleen	Lamb kidney	Strawberries
	Lamb liver	

The question of dehydration which both medically and surgically has been a *bête noir* to the profession, can be viewed with much less alarm when its chemistry is better understood. Bearing in mind that this condition exists only in the absence of sufficient osmotic tissue tension, it is imperative that this be altered to restore the proper tissue balance. In cases of inordinate tissue retention, *i. e.*, cardiac failure with edema, hepatic cirrhosis, Addison's disease, various types of nephritis, etc., all are in accord as to salt restriction. In dehydration the opposite view should be instituted and salt should be liberally administered.

It is only of recent years that the profession has come to recognize that the offending radical in salt is not that of

\* These items contain over 3 mg per cent.

chlorine but of sodium. An illustration admirably bearing this out is ammonium chloride which is recognized as being an efficient diuretic, whereas sodium bicarbonate in excessive quantities will produce a generalized edema.

A further illustration of the prompt results produced by the overingestion of salt was observed by the author in the course of gastric tube feedings in a case of anorexia nervosa. Four feedings were given daily through a duodenal tube. During the first series of treatments 1 level teaspoonful of table salt was given with each feeding with no untoward results. At a subsequent period of treatment, approximately a year later, the salt administered was inadvertently increased to a heaping teaspoonful per feeding. The clinical response was to increase the body weight 16 pounds in six days with associated physical distress. This was exhibited by severe multiple joint pains and a general water-logging of the entire body. By way of interest we happened to have control blood chlorides and as soon as the presenting symptom was suspected, a redetermination of the blood chlorides showed a marked increase.

The majority of the salt substitutes, which unfortunately have been recommended to and used by the profession, are no better than sodium chloride itself. These carry the full complement of sodium bound with some other base. Some others present a combination of both sodium and potassium which naturally reduces the total sodium intake to some degree but does not obviate the obnoxious sodium radical.

The following list presents those foods which analytically have been found to be highest in sodium in contradistinction to sodium chlorides:

#### FOODS HIGHEST IN SODIUM

Bread	Egg white	Paprika
Butter	Endive	Pepper, black
Carrots	Lima beans, dry	Raisins
Caviar	Meat extract	Spinach
Cheese	Olives	Watercress
Clams	Oysters	Wheat bran
Crackers (biscuits)		Wheat germ

All brined, corned, pickled, smoked and salted foods.

It must not be overlooked that whereas the average tuberculous patient at the time of diagnosis is generally underweight, it cannot be concluded that this is the case in all patients presenting this disease. It is well recognized that pulmonary tuberculosis afflicts the overweight in a surprisingly large number. In these instances a high caloric diet naturally is not to be observed. The caloric yield should be reduced but the protein factor should be maintained at the proposed high level.

*Tuberculous enteritis* is a common complication of pulmonary tuberculosis. Strangely, this is especially true in those cases with cavities. Some authorities believe that every cavity case with positive sputum should be looked upon as a potential tuberculosis of the intestines. In such conditions a non-residue diet is advised. This necessarily limits the administration of leafy and root vegetables and fruits which in turn almost eliminate the presence of vitamin B. Inasmuch as this deficiency affects chiefly the gastro-intestinal tract and the nervous system, it is recommended that a vitamin B concentrate be added to the diet. In a similar manner some workers believe that both vitamins C and D have a selected favorable effect on intestinal tuberculosis. This view indicates the addition of both cod liver oil and tomato juice.

It is not uncommon to encounter an associated disturbance of calcium metabolism in tuberculous enteritis or colitis, which has been observed to result in tetany or tetanoid symptoms. This necessitates specifically infiltrating into the diet, those items high in calcium which are not contraindicated due to their roughage content. Foods most readily adaptable are milk in any form and egg yolk.

In *pulmonary hemorrhage* all food and fluids should be stopped for twelve hours. During this period small pieces of ice may be given to allay thirst. After the twelve-hour period a typhoid fever type of diet should be instituted. This diet is high in caloric value, soft and high in fluids. When temperature and hemorrhage have ceased, return to the regular diet as indicated.

In *tuberculosis of the larynx* with dysphagia, the regular diet for tuberculosis as hereafter outlined, is recommended.

In tuberculosis of the larynx with dysphagia, it is necessary to plan menus which are not bulky and are bland, so that increased salivation and pain can be somewhat controlled. In severe cases the nutrition is maintained with considerable difficulty. The type of diet for this condition varies directly with the degree of dysphagia present. In brief, the diet resolves itself into one which is either fluid or semifluid in character. A practical rule to follow is that all foods which "pour" should be administered.

In résumé, the regular diet for pulmonary tuberculosis should be high caloric, high protein, to which has been added a liberal supply of all vitamins with particular emphasis on vitamins B, C and D. Additional augmentations or deprivations will depend upon the individual demands of the case at hand.

Needless to say the writer does not believe that dietary care of the tuberculous is the *sine qua non* of recovery. In the presence of the moot question of availability and assimilation of the nutritive as well as mineral content of foods, it would be foolhardy to rest upon diet alone for optimum response. The selection of proper climate, bed rest, passive and active exercise, together with corrective as well as alleviative medications in conjunction with a proper diet should produce a *tout ensemble* capable of complete restoration to health.

In conclusion, the following sample menus epitomized from the preceding material can readily be instituted for the average tuberculous sufferer.

#### Advised

<i>Meats</i>	<i>Dairy products</i>	<i>Fish</i>	
Beef	Butter	Bluefish	Oysters
Lamb	Cheese	Clams	Shrimp
Liver	Cream	Cod	Salmon
Mutton	Eggs	Flounder	Trout
Poultry	Eggwhite	Halibut	Tuna
		Mackerel	Weakfish



*Alimentary Pastes*

Bread	Pastry
Cake	Pie
Cereals	Rolls
(cooked)	
Cereals (raw)	

*Vegetables*

Beans	Peas
Carrots	Potatoes
Celery	Spinach
Lettuce	Turnips
	Tomatoes

Fruits of all characters, both fresh and stewed, should be freely utilized.

Reasonable care should be exercised in the use of the following, although their use in moderation is not actually prohibited: tea and coffee, beer, ale, in tonic doses; pork products other than bacon and smoked ham.

## SAMPLE MENU No. 1

*Breakfast:*

Orange juice (chilled)  
Oatmeal or hominy with cream and sugar  
Poached eggs on toast  
Two slices of fatty bacon  
Buttered toast  
Marmalade  
Hot chocolate

*Mid-morning:*

Milk with bread and butter

*Dinner:*

Beef broth with rice or noodles  
Broiled liver and bacon  
Creamed potatoes  
Buttered carrots  
Tomato salad with mayonnaise dressing  
Rolls and butter  
Lemon meringue pie or fruit pie  
Milk or half milk and cream

*Mid-afternoon:*

Eggnog with additional white of egg

*Supper:*

Cream of corn soup  
Vegetable plate  
Bread and butter  
Cup custard  
Milk or junket

*Bedtime:*

Hot malted milk and nuts

## SAMPLE MENU No. 2

*Breakfast:*

Chilled melon or grapefruit juice  
Cream of wheat or Pettyjohn's with cream and sugar  
Two soft boiled eggs  
Two slices of fatty bacon  
Buttered toast with jelly  
Hot cocoa

*Mid-morning:*

Milk with toast and butter

*Dinner:*

Chicken broth with noodles or rice  
Roast beef  
Baked potato with butter  
Creamed cabbage or cauliflower  
Pineapple and cottage cheese salad, French dressing  
Hot tea biscuits and butter  
Tapioca pudding and cream  
Milk or half milk and half cream

*Mid-afternoon:*

Eggnog with additional white of egg

*Supper:*

Cream of mushroom soup  
Broiled fish with butter sauce  
Buttered spinach  
Blanc-mange with cream  
Ovaltine

*Bedtime:*

Hot malted milk with white of egg and dates

## SAMPLE MENU No. 3

*Breakfast:*

Glass of grape juice or berries with sugar and cream  
Farina with cream and sugar  
Two eggs scrambled in milk  
Two slices of fatty bacon  
Buttered toast and jelly  
Hot cocoa

*Mid-morning:*

Malted milk (flavored)

*Dinner:*

Cream of asparagus soup  
Leg of lamb, mint jelly or sauce  
Fresh green peas or lima beans in butter  
Candied sweet potatoes

Avocado salad with French dressing  
Rolls and butter  
Ice cream and plain cake  
Hot cocoa

*Mid-afternoon:*

Eggnog with butter cookies

*Supper:*

Cream of tomato soup, whipped cream  
Minced chicken on toast  
Graham muffins and butter  
Fruit cup  
Milk or half milk and half cream

*Bedtime:*

Hot malted milk and raisins

The patient should not be allowed to sleep late into the morning. The breakfast hour is 8 A. M. If breakfast is served at 10 A. M. and the extra feeding given an hour later there will be little room in the stomach for more food at noon! Breakfast should be served at 8 A. M., dinner at 12:30 or 1 P. M. and supper at 6:30 P. M. The meals are to be supplemented by feedings at 10 A. M., 4 P. M. and 9 P. M. Warm milk at 9 P. M. may assist in promoting sleep. The addition of eggwhite at all times will prove efficient in increasing the daily protein intake.

When marked underweight is present it often proves efficacious to omit all water and substitute caloric yielding fluids. This is most likely to be proficient when the appetite is small or a genuine anorexia obtains.

## CLINIC OF DR. WALTER A. BASTEDO

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#### CHRONIC CONSTIPATION

CONSTIPATION is inadequacy of bowel movements, but its effects may be far-reaching, as noted by observant laymen. Henry Ward Beecher used to amaze inquirers at revival meetings by asking them, not questions about their souls or conduct, but did their bowels move regularly. He had observed that penitence was often due to constipation rather than to piety. Josh Billings rated "a good sett of bowells" higher than brains. Voltaire remarked that "A 'No' from one whose bowels move every morning is more gracious than a 'Yes' from one who is constipated."

The symptoms associated with constipation, viz., mental depression, pessimism, headache and physical inefficiency, would seem to be due either to the absorption of toxic substances formed by bacterial action, to the absorption of unchanged proteins (allergy), or to the absorption of attenuated bacteria as postulated by Adami. Of toxic substances any measurable effect is dependent chiefly upon the inability of the liver to destroy them.

The most common putrefactive poisons, skatol, indol and phenol, will produce such toxic effects in healthy men or animals by mouth doses, but only when large amounts are administered: Powers and Sherwin say 50 mg. per kilogram of body weight. In experiments done in my laboratory at Columbia by Howland and Richards and watched closely by me, indol and phenol were administered in increasing doses to dogs, rabbits, guinea-pigs, rats, and mice. The effect of a small

dose was to make the animal mope and keep away from its fellows, a larger dose made it really ill and as if it might have a severe headache, and finally a dose was reached that produced convulsions. But when the detoxifying power of the body, chiefly seated in the liver, was destroyed by minimum doses of cyanide, convulsions ensued more readily, even from an amount one-fifth or one-sixth as large.\*

In those with sluggish bowels but not pronounced constipation, the heavy head, forgetfulness and depression may diminish markedly after a free movement of the bowels, and disappear wholly in an hour or two. But the fact that this relief does not follow if the movement is of constipated type, and, after a laxative, often results before the bowels move, suggests that perhaps activation of the bowel circulation is the desideratum. When the bowel is inactive there is low activity of the liver, and, while more poison may be formed, less is destroyed (Powers and Sherwin). The proposition that the symptoms are not toxic and may be produced as a reflex by stuffing the rectum with cotton, and relieved by removing the cotton, has been shown by Ivy and others to be untenable.

The poisons themselves may cause constipation. Rettger and his colleagues at Yale (1935) have demonstrated that excised intestinal strips are paralyzed by a weak solution of indol, phenol, glutamic acid, aspartic acid or histamine, all of which may be developed by the colon bacillus. They have some evidence also that these poisons will cause depression of intestinal muscle in intact animals.

**Physiology.**—The haustra of the colon are for retarding purposes, and propulsion through the colon is accomplished mainly by *mass movements*, which occur only a few times a day. In these the haustra suddenly disappear for a length of several inches, and the contents form a cylinder or bolus that hurries forward for many inches or even a foot or two in a fraction of a minute. It is by such occasional propulsive move-

\* For discussion of these experiments see Herter, C. A., "The Common Bacterial Infections of the Digestive Tract." The Macmillan Co., 1907, p 248 et seq.

ments that the descending and iliac segments of the colon become filled, while the contents are kept from passing into the rectum by the musculature of the sigmoid-rectal junction. The descending and sigmoid portions of the colon have little power of absorption and serve for storage, so that defecation is deferred to once or twice in twenty-four hours. In normal persons the rectum remains empty or nearly so till toward the onset of defecation, for feces in the rectum give the desire to go to stool. But in some of the constipated the rectal threshold of sensation is raised so that the feces may lie in the rectum unknown to the patient and continue to desiccate. The rectum is more absorptive than the iliac colon above it (Steggarda).

During almost the entire twenty-four hours the *function of the colon is not to propel but to retard*, so that the liquid received by the cecum becomes formed stools. When the colon does propel its contents, the method employed is a mass movement and not the ordinary form of peristalsis.

**Retarding Mechanisms.**—The normal ones are: (1) the terminal ileum and ileocecal sphincter, (2) the haustral constrictions of the transverse colon, (3) the tonic rings of the descending colon, (4) the narrowed rectosigmoid junction, and (5) to hold back rectal contents, the valves of the rectum and the anal sphincters. If the contents are too liquid these natural restrainers fail to function as such; with contents too dense they overretard.

**The Bowel and Liver Circulation.**—Little is known concerning the relation of the bowel circulation to the activities of the bowel itself. The actively contracting bowel has a vigorous circulation, the dilated bowel a stagnant one. Carnot and Glénard expressed the opinion that the main factor in increasing the activity of the bowel is an increase in the blood flow through its muscle. Anemia probably has the effect of a sluggish circulation.

Mall demonstrated that the intestine is the propulsive organ for the portal blood and the intestinal lymph. Every contraction of the intestine forces blood into the portal vessels and goes to maintain the current through the liver, and, as a

consequence, the activity of the liver. The portal blood is increased in volume by the fluid absorbed from the intestines. Cathartics that begin to act high up in the small intestine, such as castor oil and calomel, have most effect on the liver circulation; those whose activity is largely confined to the colon, as cascara and senna, have probably a minor effect.

**Causes of Constipation.**—Without going into detail we might say that in most cases either (1) the mass movements fail so that the contents are held unduly long with resulting abnormal desiccation (atonic constipation); (2) the colon is hyperirritable and goes into spasms which effectually block progress (hypertonic or spastic constipation); or (3) there is damming up in the rectum (rectal constipation).

#### TREATMENT

People naturally not constipated pay little attention to their bowels, frequently go to stool at irregular times, skip a day now and then, have loose movements at one time and hard ones at another, and have occasional foul smelling stools or attacks of gas. But they give minor heed to these irregularities. The constipated, on the other hand, may become "bowel conscious" and then are upset by any departure from what they assume to be normal. Moreover, many of them suffer from mental and physical inefficiency whenever they fail to have adequate movements. It is for these reasons that they seek help. Physicians frequently tell these patients, "There is no harm if you skip a day," but every constipated person knows that this is not true.

From the patient's standpoint, adequacy of bowel movements means stools that are passed at least once a day with ease and comfort and with the sense of complete emptying. This, then, is our aim in treatment. But the aim is not attained if our remedies go to the other extreme and cause loose or frequent stools, for these also arouse bowel consciousness and are incompatible with bowel health.

**Any surgical condition** that may have a direct influence on the bowels should be attended to, such as cholecystitis, appendicitis, salpingitis, rectocele, etc.

**Rectal Constipation.**—If on examination a substantial amount of feces is found in the rectum but the patient has no desire to defecate, or if the patient has the desire but cannot succeed because of some rectal or anal condition, the constipation is rectal. If this is due merely to the lower end of the stool becoming dried out and scybalous, so that defecation is difficult and irritating to the anus, it may be corrected by mouth doses of mineral oil. If the fault lies in irritated crypts, painful hemorrhoids, fissure of the anus, or prolapse, conditions commonly encountered, mineral oil by mouth will ensure soft feces; and the insertion of 60 cc. (2 ounces) of olive or corn oil at night, to be retained till morning, will often allay anal spasm, permit a satisfactory movement, and promote healing. Such an amount of oil can be injected readily by the patient with a soft rubber ear syringe. In addition, on arising or at other times, an anesthetic ointment of 5 per cent of ethyl aminobenzoate in petrolatum album may be inserted as far as possible into the anal opening. If these simple measures do not relieve, one needs the help of a proctologist.

**Constipation with Site Above the Rectum.**—The stock advice is about as follows: whether you feel like it or not, try to have a stool every morning about the same time. When the desire to defecate comes do not postpone going to stool. Take plenty of exercise. Drink freely of water.

**Exercise.**—This does not necessarily help the bowels. Of 745 athletic students Forsythe found 10 per cent taking laxatives, and of 100 engaged in maximal competitive athletics 18 per cent. At Columbia, among the students in required gymnasium work, Meylan found 30 per cent constipated. A number of my constipated patients have been college or professional athletes, gymnasium instructors, horsemen who spend much of their time in the saddle, and others doing hard physical work or engaging constantly in sports. On the other hand, many of sedentary habits have no constipation.

By roentgenologic study, Case and others have observed slight progress of the colon contents from vigorous abdominal exercises, but as a rule exercise is without effect on the motility



of the colon. Its value, especially if taken outdoors, lies essentially in improvement in the general vitality and of the appetite, so that the subject eats more. Whether or not special exercises for the abdominal muscles help more than general exercise there is some doubt, but one might favor such home exercises as deep diaphragmatic breathing, working the abdominal muscles in and out with the chest set, raising the knee sharply to hit the abdomen, and raising the legs while lying on the back.

**Massage** is sometimes substituted for exercise. But during roentgenologic examination, with deep pressure directly on the colon, Case found it impossible to force the contents of the ascending into the transverse colon, or of the transverse into the descending. In the very thin walled, where he could grip the colon heavily with the fingers, he could effect only a slight movement of the contents. In the gas filled colon only, could he shift the bolus several inches. In thin persons Alvarez could not push along the feces in the left colon. Groedel was unable to move the contents with a vibrator in full action. As the colon contents are propelled essentially by only occasional mass movements, it would seem that the value of massage lies either in the (improbable) production of a mass movement or in promotion of the circulation.

**Water.**—Plenty of water with the meals may hasten the arrival of the food residues at the cecum, but the large bowel does a lot of absorbing. In a number of nondigestive patients in bed I found that the ingestion of a glass of water every hour for fourteen and fifteen hours daily for one week, almost a gallon a day, did not increase the bowel movements and served merely to activate the kidneys. On the other hand, too little water may result in feces of a dried out, constipated type, especially when the contents are held in the colon unduly long, as in the constipated. Though the various foods supply a great deal of water, this is practically all necessary, according to Rowntree, for their own digestion and metabolism, even in the case of milk (Sherman excepts fruits). Therefore, besides liquid foods, extra water must be taken. However, Cowgill

*et al.*, warn that excessive amounts of water deplete the body of vitamin B, which is a necessary element for appetite and bowel tone.

**Foods.**—The following sections on Foods and Bulk Producers are abstracted from the author's article in the Review of Gastro-enterology, 2:4:279, Dec., 1935:

The cause of normal defecation is food, for a bulk of undigested residue sufficient to produce distention is requisite if the bowels are to move properly. From foods ordinarily eaten the large intestine is subject: (1) to distention—by bulk of residue; (2) to mechanical stimulation—by indigestible roughage, such as bran, husks, fibers, seeds, skins, etc.; (3) to chemical or drug action—by laxative acids and their salts, as in fruits, by free fatty acids and soaps formed from the oils and fats, by other acids, by sugars, by volatile oils, by the oils and resins of spices, and by other chemical substances, among which must be included those produced by the activities of intestinal bacteria; (4) to the influence of vitamins, especially vitamin B; and (5) to allergic reagents.

**Fats and Oils.**—These tend to be laxative, but cannot always be tolerated in large amounts. Moreover they rob the organism of calcium with which they form insoluble soaps, and these soaps adsorb and carry out certain products of digestion (Teller). In so far as they liberate fatty acids or form soluble (sodium) soaps, fats are irritant.

**Food Residues.**—Some are bland or smooth, *i. e.*, mechanically unirritating, while some are believed to act as mechanical irritants and are called roughage. Hence *residues may be classed as bland residues and roughage*. Foods that leave a fair amount of bland residue are: milk, cheese, egg, particularly raw egg, white bread, macaroni, the branless cereals and potatoes. The foods on which we depend mostly for roughage residues are: the bran-containing cereals, graham and whole wheat breads, and most fruits and vegetables, especially the raw fruits and the salads and relishes. The roughage of fruits and vegetables is composed of the tissues held together by woody and bast fibers, corky epidermal tissues, seeds, hard substances

like the stone cells of pear, and other tough or hard indigestible parts. This roughage is sometimes mistakenly called "cellulose," but cellulose itself is a very bland carbohydrate with formula,  $C_6H_{10}O_5$ .

Rubner found that the feces of a mixed diet gave 100 Gm. of water and 35 Gm. of dry substance, while those of a vegetable diet gave 260 Gm. of water and 75 Gm. of dry substance. Thus residues increase the amount of feces, not alone by their own bulk, but also by the water that they carry. But the indigestible residues are not all available to move the bowels, for they are prone to undergo bacterial decomposition, especially in the constipated (Rose, Cowgill). Some of the bacterial products stimulate the bowel wall; others, such as indol and phenol, depress it. Cowgill and Sullivan ascertained that habitually constipated persons require nearly twice as much roughage for colon stimulation as normal people.

Weight for weight, most fruits are more laxative than even coarse vegetables, for the fruit juices contain laxative salts or form them in the duodenum. Indeed, many people who would otherwise be constipated keep to normal movements by a very moderate daily allowance of fruit, such as an orange, an apple or a dish of prunes.

In the feces of normal dogs I have found much coarse grass, hair, gravel and pieces of bone. Hoelzel mixed screws, corrugated wire and rough pieces of gold and silver with the daily diet of laboratory animals for months at a time without noticeable harm. In fact, he observed more marked lesions in the intestines from an inadequate diet. In stools from humans I have found hard seeds and much coarse food in chunks and tangled fibers, without apparant bowel stimulation or excess of mucus. Thus there is lack of proof that roughage causes pathological irritation of the bowel, and there is much evidence that the normal digestive tract can bear vegetable and even mineral roughage in large quantities without apparant harm. In many instances even large quantities of roughage do not cause the bowels to move. Therefore, the term roughage does not of necessity convey the idea of irritation, and some physi-

cians become unduly alarmed when their patients eat freely of roughage foods.

On the other hand, in the presence of a sensitive stomach or a hyperirritable bowel, and these are common in the constipated, roughage tends to irritate, and may produce hyper-tonic (spastic) constipation. In such a condition bland foods with the addition of bulk-producing drugs and perhaps mild chemical laxatives will do more good and less harm than coarse indigestible roughage foods. Whether or not roughage itself is a cause of hypersensitiveness remains an unsettled problem; but it is agreed that, under the influence of rough foods, a latent hyperirritability may become active.

*Bran* owes its laxative properties largely to its fiber, but, as "commercial bran" is difficult to take, the steamed or processed bran, which has softer fiber and mixes better with the contents, is the preparation offered for humans. This is less irritating but less laxative than commercial bran. Experiments on normal and constipated people have demonstrated that bran in quantities of 30 Gm. (1 ounce or about 5 tablespoonfuls) a day tends to make larger and softer movements, but usually not loose movements.

Osborne and Mendel found bran irritant to both stomach and intestines. Mann's gastrectomized dogs vomited when bran was added to their cereal diet. In Hoelzel's rats bran caused an undue proportion of infective lesions in the cecum, and in one case a perforation. On the other hand, Rose *et al.*, found no intestinal lesions in 22 rats that had been fed bran for two to four months. There have been a number of instances of obstruction of the human small or large intestine by bran balls. When the colon is hyperirritable, bran may create distress and cramps.

Some of the value of bran has been attributed to its vitamin B, but the amount of this is not great. Bran holds only about 24 per cent of the total vitamins of the whole wheat grain (Mendel and Lewis) and is about one fifth as rich in vitamin B as the wheat germ (Rose *et al.*).

Many administer bran in the form of graham or whole

wheat bread, or the natural bran-containing cereals. Cooked in these forms it is less harsh, and consequently less laxative, than even processed bran. But, according to the figures of the United States Department of Agriculture for the several flours, to obtain the daily 1 ounce of bran, one would have to consume 10 ounces of graham bread or 20 ounces of whole wheat bread, and the bran would be in its least laxative form. Of shredded wheat, five biscuits represent the fiber of about 1 ounce of bran.

To summarize, bran administered by itself is not a food but is probably an irritant drug, to be classed with cathartics. When cooked in its natural admixture with the other constituents of grain it is less irritating and less laxative. It is possibly useful when there is habitual lack of roughage in the diet, but it cannot be furnished in adequate dosage by graham or whole wheat bread. It is contraindicated in such irritative conditions as gastric hyperacidity, colonic hyperirritability and mucous colitis.

**Bulk Producing Drugs.**—There is no line of division between foods and drugs and we pass readily to those drug substances prescribed to add bulk to the colon contents.

*The bulk producers* are of two kinds, the *bland* and the *roughage*. The bland group includes agar, bassorin, tragacanth, hulled psyllium seed, cellulose and mineral oil. The roughage group is represented by whole psyllium seed and flaxseed. All the bulk producers increase the bulk and the softness of the colon contents, not so much by their own volume, but largely through their ability to carry down water and hold it against the absorptive powers of the colon. All except mineral oil are dry and must be accompanied by abundance of water. Nearly all of them make a viscous mucilaginous substance that in large amounts may have detrimental effects throughout the alimentary tract. Mostly they do not hasten passage through the tract, but merely make the stools softer and bulkier. They do, however, carry down the residues with greater uniformity.

As the dry bulk producers are all prescribed by spoonfuls and differ markedly in weight, comparisons must be made on a volume dosage, and not on that of weight. Therefore, of

several of them I have taken one measured drachm of the dry substance and measured it after it had soaked in water for twelve hours and the surplus water had been drained off. If the wet bulk of a given measure of dry flaked agar saturated with water is represented by 1, that of granulated agar is 3, of powdered agar  $5\frac{1}{2}$ , of whole psyllium 10, of hulled psyllium 14, and of bassorin 29. The agar are rather dense and coherent, the bassorin stools soft, and interspersed with jelly-like particles, while those from both whole and hulled psyllium are of a tenacious, tough and rubbery consistency that suggests difficulties for the churning and absorptive functions of the bowel. From hulled psyllium we have seen a stool in a single elastic piece 15 inches in length. The stools of whole psyllium regularly contain many unchanged seeds, which constitute roughage.

*Mineral Oil.*—This valuable softening agent does not coat the intestinal wall to serve either as a protective or as a lubricant, but is mixed with the contents, usually in emulsified form. Its stools contain much more water than normal (Newman and Gruenfeld, Schlagintweit), so it is a bulk producer. It proves especially valuable in conditions of hyperirritability of the bowel, in hemorrhoids or other anal irritations, and in those whose feces tend to form conglomerates or hard scybala. In intestinal toxemia it may be beneficial by carrying out some of the oil-soluble poisons of putrefaction, notably indol, skatol and phenol.

But mineral oil is not harmless, for it coats the particles of food and retards their digestion, it interferes with the absorption of the products of digestion and, according to Mellanby, it prevents the reabsorption of bile from the intestines. But more important still is the fact that it is practically unabsorbable by the bowel and consequently carries from the body some of the substances that are soluble in oil, such as the vitamins A, D and E. DaCosta and Carlson report that adult rats on mineral oil failed to reproduce owing to the depletion of vitamin E. Dutcher *et al.*, Rowntree, Jackson and others have found that mineral oil, in doses comparable with those given

to humans, killed rats on a minimal vitamin A diet. The possibility of mineral oil creating avitaminosis in the debilitated, in nursing mothers and in growing children cannot be ignored.

Yet it has been found that depletion can be avoided by a moderate increase in the butter fat, and by administering the oil separately from the food. In butter fat vitamin A is represented largely by its precursor, carotene, which has more affinity for mineral oil than for the lipids of the intestinal contents. The opposite is true of vitamin A itself. With cod liver oil and its concentrates, mineral oil results in no appreciable loss of vitamin A.

**The Chemical Laxatives.**—Hurst writes, "An excessive quantity of coarse indigestible food probably does more damage to the mucous membrane (of the bowel) than a mild chemical irritant." In chronic constipation, the useful drugs are limited in number, those employed being mostly small doses of the saline cathartics (especially the mineral waters and milk of magnesia), the tonic laxatives or anthraquinone drugs (cascara, senna, rhubarb, aloes and aloin), and phenolphthalein. Any of these may cause griping, especially in a hyperirritable colon. The salines produce abnormal stools and cannot be continued indefinitely. Phenolphthalein is partly absorbed and some of it is reexcreted in the bile, therefore its action tends to be prolonged, and it is more prone than the tonic laxatives to make undesirable loose stools. This is especially the case with its mineral oil admixtures. Aloes is harsher and more active than aloin. Rhubarb is very mild. The drastics, such as jalap, colocynth, gamboge, scammony and podophyllin, which irritate the entire digestive tract and may produce inflammation of both the alimentary tract and the kidneys (drastic action), are not applicable in chronic constipation.

There are undoubtedly many instances where the use of chemical laxatives is a necessity, at least for a time. When hyperirritability does not predominate, the tonic laxatives are most useful remedies. Their chief action is on the large intestine. They do not produce inflammation in the intestines,

and if their active principles are absorbed the kidneys are not injured. They may be taken for years without the need to increase the dose; indeed often this may be reduced gradually till the drug is dispensed with altogether or needs to be taken only occasionally.

We have found particularly useful the preparations of agar and bassorin with cascara. Another well-tried prescription of the author is: *sodii bicarbonatis*, 12 cc. (3 drachms), *fldext. cascarae*, 8 cc. (2 drachms), *mist. rhei et sodae comp.*, N.F. q.s. ad 120 cc. (4 ounces). M. et Sig. Two teaspoonfuls with a glass of water an hour before lunch and dinner and at bedtime. This is the empty time of the stomach, a better time for the administration of an antacid mixture than at meals. Frequently it is not long before half the amount is effective, and shortly thereafter the bedtime dose alone, or a dose once a week.

A palatable remedy of which a small dose may be taken before or after each meal is:  $\mathcal{R}$  *fldext. cascarae aromat.*, *fldext. sennae*, *tinct. rhei aromat.*, of each equal parts. It may be made up to teaspoonful doses with the vehicle, *isoalcoholic elixir*, N.F.

**Enemas.**—These may be used occasionally, and if atony of the rectum or lack of sensitiveness cannot be overcome may have to be employed indefinitely. I have encountered two persons who had used a daily enema for some forty or fifty years and seemed in good general health. The roentgen use of the barium enema, which is denser and more viscous than a normal enema, has demonstrated that under two feet of pressure such an enema reaches the cecum in two to five minutes, that as a rule 1000 to 1500 cc. will fill both colon and rectum, that not infrequently there is a leakage backwards into the ileum, and that at the subsequent defecation almost the whole colon except the cecum, and at times the cecum also, may be emptied almost completely. Such an extensive filling and emptying for defecation is unphysiological. After a barium enema, roentgenologists have frequently noted spasms and undue activity in some part of the large bowel, but mostly these occur only in patients with hyperirritable colon.



Except in rebellious cases the enema should not contain irritants such as soap. In 6 of 20 men to whom 0.5 per cent soapsuds enema was administered by Runge and Hartman, occult blood appeared in the stool within three days; and in all of 16 rabbits an enema of the same soapsuds caused ulcerations and diffuse ecchymoses. Alvarez states that powerful contractions are produced when the colon is filled with soap water and then tied off a little above the anus. With the sigmoidoscope, I have seen marked hyperemia following a soapsuds enema, a condition that I have never encountered after an enema of plain water or physiological salt solution, which may be considered the proper liquids for ordinary use.

**Finale.**—If we believe that constipation has profound effects upon the efficiency and the disposition we cannot feel that we have fulfilled our responsibilities by a mere laxative prescription. Always the general vitality and appetite should be promoted. All should be water drinkers. In a goodly number satisfactory movements may be continued indefinitely as the result of improved diet habits; in others, food regulation alone does not suffice. In many instances, the treatment is simplified by the use of bland bulk producers; yet, if required in large amounts, these have deleterious effects on all the digestive processes and result in stools that are far from physiological. As time goes on we learn that in some of our patients both foods and bulk producers eventually fail, and the good results can be maintained only by chemical laxatives; indeed, chemical laxatives, properly used, together with food regulation, may lead to cure. In still others completely satisfactory movements are not obtained no matter what measures we try. By long experience we become convinced that some people are so unendowed by nature that they cannot be cured and must depend on laxatives throughout life.

No permanent benefit results from medication "as necessary," for the result of this is a large dose one night because the bowels have not moved enough, and a small dose or none at all the next night because they have moved too much. This

procedure never results in cure. Of artificial aid the bowel should receive the same each day.

A fairly large percentage of constipated patients have hypersensitive digestive tracts, which render them unable to take with impunity even the normal amount of roughage, or even, perhaps, fruit juices. They require bland food, bland bulk producers and carefully selected chemical laxatives. Sometimes belladonna or atropine is a valuable addition. Frequently with their constipation these patients manifest psychic disturbances, gastric hyperacidity, hyperirritable colon or mucous colitis, conditions that present complex problems for management.\*

In any event experience teaches that because of undesirable reactions from coarse indigestible foods, of stomach irritation from acid fruits, of a distaste for vegetables, of rebellion over the long continued use of bulk producers, or for some other reason, many will eventually return to the chemical drug laxatives, and frequently to patent medicines. Let us not precipitate this crisis ourselves by prescribing at the outset proprietary mixtures with trade names, under which the patient learns to purchase them over the druggist's counter.

\* Bastedo, Walter A.: Functional Disorders of the Colon, Mucous Colitis, *MED. CLIN. N. AMER.*, vol. 18, No. 3, pp. 883-910, November, 1934.



## CLINIC OF DR. M. JOSEPH MANDELBAUM

FROM THE BRONCHOSCOPIC CLINIC, HOSPITAL FOR JOINT  
DISEASES

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### ASTHMA: TREATMENT BY INTRATRACHEAL INJECTION OF IODIZED OIL

With an Analysis of 1000 Compiled Cases (Including 114 Newly  
Reported Cases)

FEW diseases have had a greater number of remedies offered for their cure than asthma. While in a certain number of cases, a few of these means have had a palliative effect, such as temporarily reducing the severity and even the frequency of the paroxysms, still fewer have successfully run the gauntlet of time and experience. Most have been eventually thrown into the discard, with perhaps epinephrine alone, among the modern remedies presented for the treatment of this very distressing disease, remaining outstanding in its influence, though, also, mainly in a palliative manner. In one other group of asthmatics, a limited group of allergic origin, desensitization has occasionally proved of value, but this has usually required repeated seasonal administration. Therefore, whenever a new remedy presents itself for consideration, and particularly if repeated favorable reports are noted, as in the use of intratracheal instillation of iodized oil, further investigation is warranted.

The increasing interest in and use of the intratracheal injection of iodized oil for asthma is the stimulus for this paper, which comprises a critical study of almost all of the papers already published and of several as yet unpublished articles

which, through the permission of the authors, have been included in the statistics of this report, as well as of 114 cases of my own, the total number of cases represented being 1000.

**Sources of this Compilation.**—The following are the sources from which the 1000 cases herein reported were obtained:

Refer- ence.	Year.	Author.	Number of cases reported.
1	1932	Taylor, J. H.	2
2	1932	Fink, L. W.	13
3	1932	Anderson, W.	60
4	1933	Cole, D. B. and Harper, E. C.	26
5	1933	Alison, J. P.	10
6	1933	Harris, M. C. and Turkel, H. L.	50
7	1934	Balyeat, R. M. and Seyler, L. E.	100
8	1935	Balyeat, R. M. and Seyler, L. E. and Shoemaker, J.	50
9	1936	Penta, A. Q.	50
10	1936	Anderson, W.	300
11	1936	Mandelbaum, M. J.	114
12	1936	Watnick, J. S.	2
13	1936	Combined smaller groups of 1 to 3 cases	223
			1000

The direct intratracheal instillation of various medicaments for divers bronchial affections is not new, however, for, as I recalled in a previous paper in 1932<sup>14</sup> nearly one hundred years ago Horace Green,<sup>15</sup> of New York, had already instituted the intratracheal instillation of remedial agents for therapeutic effect. Although many others, notably of the French School, reported on the use of direct intratracheal therapy during the century just mentioned, it was not until Forestier and Leroux's announcement in 1922<sup>16</sup> that iodized oil was a safe bronchographic medium, that a new and widespread interest in this method was reactivated.

In 1924,<sup>17</sup> the author devised a styletted catheter for instilling iodized oil into the trachea and in 1928<sup>18</sup> published a description of a finger-holder for a laryngoscopic mirror which made it possible for the operator to introduce fluid media into the trachea positively, safely, and with comparative ease.

**Review of Literature.**—Before presenting the cases and the method used by my associates and myself, let us review as briefly as possible the literature of direct intratracheal therapy before the advent of iodized oil.

Horace Green<sup>15</sup> began the use of direct intratracheal injections of solutions of silver nitrate for pulmonary tuberculosis and other forms of bronchopulmonary disease in 1835. In the succeeding decades, others contributed to the subject of direct intratracheal injection of therapeutic media for various bronchopulmonary affections, as follows: Alison in 1853,<sup>19</sup> Fullgrave in 1885,<sup>20</sup> Willis Anderson in 1900,<sup>21</sup> Delor in 1901 to 1902,<sup>22</sup> Tiphine also, in 1901 to 1902,<sup>23</sup> Willis Anderson again in 1902,<sup>24</sup> McKinney in 1903,<sup>25</sup> Richardson in 1904,<sup>26</sup> Meltzer in 1912,<sup>27</sup> Winternitz and Smith in 1919<sup>28, 29</sup> and in 1920,<sup>30</sup> Boirac in 1920,<sup>31</sup> Lehmann in 1922,<sup>32</sup> Castex<sup>33</sup> and Mitelette in 1924,<sup>34</sup> Marty in 1925,<sup>35</sup> and Pare in 1927,<sup>36</sup> Turner in 1928,<sup>37</sup> Mounier-Kuhn in 1928,<sup>38</sup> Menager in 1929,<sup>39</sup> Pallesiini and Albanese in 1931,<sup>40</sup> and Spoto in 1931.<sup>41</sup>

In 1923, Forestier and Leroux<sup>42</sup> reported further on the value of intratracheal injections of iodized oil. Subsequent investigators noted that a beneficial therapeutic by-effect resulted from the use of iodized oil in a variety of bronchopulmonary diseases.

For those interested in a consideration of iodized oil from the historic, therapeutic, and bibliographic standpoints, Sicard and Forestier's work,<sup>43</sup> *The Use of Lipiodol in Diagnosis and Treatment*, is recommended. American literature is too replete with excellent bibliographies regarding the use of iodized oil for both diagnostic bronchography and as a therapeutic medium in conditions of the bronchopulmonary tree other than asthma. for a full list here. Pritchard, Whyte and Jordan,<sup>44</sup> in 1926, and Ochsner in 1926<sup>45</sup> and again in 1929,<sup>46</sup> called the attention of the profession to the beneficial effects following the intrabronchial injection of iodized oil in various types of bronchopulmonary disease. But Taylor<sup>1</sup> and Fink<sup>2</sup> and Willis Anderson<sup>5</sup> in 1932 were the first to publish papers in the United States on the use of iodized oil in bronchial

asthma by intratracheal injection. Taylor, in June, 1932,<sup>1</sup> cited 2 cases of bronchial asthma, which, after the therapeutic instillation of a number of iodized oil treatments, showed definite improvement with a reduction of the frequency of the asthmatic seizures.

In August, 1932, Fink<sup>2</sup> published the results of the use of intratracheal injection of iodized oil in 13 cases of bronchial asthma, and stated his conclusion that results were in proportion to the extent and duration of pathology.

In November, 1932, Anderson<sup>3</sup> reported the first large group of cases—60—of bronchial asthma, in which iodized oil only (lipiodol) was the medium used by intratracheal injection. A considerable number of these cases had suffered from childhood, and most had been afflicted for more than four years. Anderson's research extended over seven years. About one half of these cases were allergic in nature and the other one half were activated by peripheral, psychic or acute infectious respiratory causes. Satisfactory results were reported in all of the cases. Twenty-four were completely relieved from one to five years; the remaining 36 were definitely relieved following treatment from three to twelve months.

Cole and Harper, in April, 1933,<sup>4</sup> reported 26 cases of bronchial asthma treated by iodized oil injections. Fourteen were markedly improved; 12 were benefited in varying degree. Cole and Harper stated that all cases had been improved, that none showed any ill effect, and many had been relieved of their asthmatic attacks after the initial treatment. In this year, Alison<sup>5</sup> also reported 10 cases of bronchial asthma treated by the use of iodized oil, in all of which excellent results were obtained. Harris and Turkel<sup>6</sup> likewise in this year began the use of iodized oil for asthma. These authors selected 50 of the most difficult cases they could find in two separate institutions, as well as in private practice. Lipiodol was the form of iodized oil used. They made a particular study of the etiologic factors in their series, classifying the cases as follows: 20 as infectious, 8 as allergic, and the remaining 22 as giving evidence of focal infection associated with a history of

clinical hypersensitiveness substantiated by skin tests. The ages varied from twenty-two to sixty-four, and all had received routine continuous treatment subsequent to the iodized oil instillation for a minimum of three years. In 4 cases, the results were excellent, *i. e.*, after several months of treatment the patients remained asthma-free for more than a year and a half. Eight cases obtained little or no relief; 14 were partially relieved; 28 were relieved; 75 per cent or better.

Anderson reported in 1936<sup>10</sup> a total of 360 cases of asthma treated with iodized oil, combining in his summary the 60 cases originally published<sup>8</sup> and 300 patients subsequently treated by this method. Not only has he had the largest experience with this method, but the excellent results he has obtained have undoubtedly been due to meticulous study he makes of his cases as well as the great caution he exercises, particularly in the serial mode of injection of the various lobes. He first injects one lower lobe, then one week later the opposite lower lobe, to determine the presence and location of tubal obstruction. The lower lobes are injected first inasmuch as these are most frequently involved. In his cases bronchiectasis was not usually extensive. The oil, Anderson states, should reach the alveoli in from seven to fifteen minutes. If not, complete or partial obstruction is present; this obstruction being due, in his opinion, to bronchospasm, edema of the mucosa, or excessive secretion. To differentiate, a hypodermic of 10 mm. of adrenalin is given one-half hour after the injection and the patient examined fluoroscopically. If the obstruction is due to bronchospasm, it will have been relaxed by the adrenalin or the edema thereby reduced, so that the oil will have descended into the vesicles. Ten to 20 cc. is generally sufficient for one lobe. After the initial injection, both lobes may be injected simultaneously, for which 20 to 30 cc. may be required.

If the oil does not pass quickly into the alveoli, it will be expelled more rapidly, much within twenty-four hours, when subsequent injections may be given more frequently, with safety. Dependence upon the rate of expulsion of the oil,



which varies in the individual case, is important, as otherwise overloading of the tissues may ensue. At no time should the amount of oil be sufficient to reduce the vital capacity more than 50 per cent; this may induce more severe and more frequent attacks, even severe cyanosis. When oil promptly reaches the alveoli, indicating freedom from excessive secretion, the amount of oil injected and the frequency of injection should be diminished. If no improvement is seen after several injections into lower lobes and one is assured that the oil has reached the alveoli, one lobe at a time should be treated and effect noted. If no relief follows, treatment is continued until the entire bronchial tree has been washed out with the oil until improvement has resulted, unless some contraindication should arise. Response varies. Some patients respond immediately, others gradually, and some not for many months, when sudden improvement is noted. The young respond more rapidly, as a rule, than the old; those whose asthma followed a respiratory infection such as bronchitis, whooping cough or pneumonia, measles or influenza, respond more slowly than the allergic types. Ninety per cent of the cases of asthma complicated with bronchitis were rapidly relieved of the latter. Reduction of clinical sensitiveness to excitants and stimuli was also noted. In some, clinical sensitiveness promptly disappeared, although skin tests remained positive. A reduction of 75 per cent in susceptibility of these asthmatics to colds was noted, following iodized oil treatment.

Penta, in 1936,<sup>9</sup> reported that in a series of 50 cases of bronchial asthma treated over a period of six months with instillations of lipiodol, 40 per cent obtained a symptomatic cure; 25 per cent have shown definite improvement as manifested in the greater interval between the attacks as well as in the marked reduction of severity. The remaining 30 per cent have shown little or no improvement. Penta's routine is to instill the oil (20 cc.) every week for a period of two months and then gradually increase the interval between treatments, individualizing cases. At the end of the fourth month most of his cases were receiving the oil only once monthly.

**Author's Cases.**—The following 114 cases reported by the writer of this paper comprise an unselected series from hospital and private practice over a period of ten years and upon an experience of twelve years in the practice of direct intra-bronchial therapy.<sup>14</sup>

Total number of cases treated	114
Total number of cases unable to follow-up	17
Total number of cases with follow-up to date	97
Total number of cases with complications	4
Total number of deaths	0
Sex: males 86; females 28.	
Youngest patient: eight years; oldest, seventy-seven years.	
Least number of injections needed to relieve, 1 (in 3 cases).	
Maximum number of injections needed to relieve, 84.	
Average number of injections given	37
Average duration of treatment	5 months
Average amount of iodized oil used in successful cases	684 cc.
Maximum amount of iodized oil used in any case	840 cc.
Average intervals of treatment, six days.	
Longest period of treatment: two years and four months.	

Of the 38 cases treated in the first five-year period, 9 had recurrences: 2 in the sixth year, 3 in the seventh year, 1 each in the eighth, ninth and tenth years. Upon resumption of treatment, 7 of these 9 recovered quite promptly. The other 2—1 recurring two and the other three years after the original series of treatments were completed—continued to have asthmatic paroxysms, though not nearly so severe or as frequent as formerly.

Bronchograms were made in 76 cases. Of these, 36 had definite bronchiectasis in varying degrees. In 23, the demonstrable bronchiectasis was limited to the lower lobes. In 5 cases, only the right lower lobe was involved; in 10 cases, both lower lobes; in 2 cases, only the right middle lobe. In the other 6, combinations of lobes, mostly lower and middle right, were present. In only one instance was an upper lobe alone involved, the right. In 2 cases, the lower left and middle right were affected.

The bronchiectasis was mainly of a cylindrical type. In a few cases only was it saccular. In approximately one fourth

of the cases it was of a mixed type, *i. e.*, combined saccular and cylindrical. Only 1 case of asthma due to foreign body was found in this series. The patient was a boy of ten years with a small piece of peanut kernel in the upper left main bronchus; when this was removed he promptly recovered.

Of the 97 cases with a satisfactory follow-up, only 32 have been free from attacks long enough to be classified as cured, that is, with no recurrences and no treatments of any kind for three years or more. Of the remaining 65 cases, 38 were only slightly relieved or not aided at all after nine months of treatment and the other 27 cases are still under treatment. In the latter group, 11 who have been under treatment for more than eight months are definitely improved.

Of the 97 faithful to treatment, 18 reacted to the various allergens, mainly the pollens, a few to dust alone, and about one quarter to both dust and pollens. Of these, 14 had received prolonged desensitization treatments without any relief of their paroxysms, while the others who reacted positively to allergens had had no allergic treatments. Eleven of the 97 had nasal polyposis in varying degree. Approximately one half of these patients (5) were relieved only after the iodized oil injections were resumed following removal of the nasal polyps. The remaining 3 were not relieved either before or after the polyps were removed.

Direct bronchoscopic cultures were taken in only 19 cases. These showed a variety of organisms and the results of the treatment by iodized oil were not seemingly affected by the nature of the bacterial flora.

Twenty-five cases had paranasal sinusitis, 16 of whom improved only after sinus treatment.

**Contraindications.**—In patients sensitive to iodine, developing marked local effects or rashes or other constitutional or local symptoms following its therapeutic administration by any method, iodized oil should be used very cautiously and, then, in very small amounts only. Those definitely susceptible to iodism should not be subjected to any form of iodine therapy. Anderson<sup>10</sup> believes that all prospective patients for

this form of treatment should be previously tested for iodine sensitiveness.

Treatment with iodized oil should not be instituted in patients whose asthmatic attacks are due to growths within or without the bronchi. Most observers believe that a considerable percentage of asthmatics are suffering from certain etiologic factors which, while they produce asthmatic seizures, are only curable in some instances by removal of the cause. Thus, individuals with either intrabronchial or intrapulmonary neoplasms determinable only by roentgen and bronchoscopic study, would not be proper subjects for the use of iodized oil treatment even though these conditions be associated with asthmatic paroxysms. Malignancies, particularly carcinoma, must always be thought of, as well as nonmalignant neoplasms of the bronchopulmonary tissues. Other lesions causing obstruction to free bronchial drainage, whether foreign bodies causing obstruction to free bronchial drainage, or abscesses, tumors, cicatricial distortions, etc., mediastinal growths, pleuritic effusions or neoplasms, causing extrabronchial pressure—all are to be kept in mind, particularly during the early stages of so-called "asthma." This type of treatment should not be undertaken, moreover, in cases of acute pulmonary abscess, severe hemoptysis, or in patients with unknown causes of fever or in the acute stages of grippal respiratory disease in either the upper or lower air passages.

**Anesthesia.**—Anderson<sup>10</sup> uses no preliminary morphine or other sedatives. Most writers agree that both the cough and swallowing reflex must be completely abolished during the treatment. This is accomplished by means of a variety of local anesthetics. Anderson sprays the pharynx and anterior and posterior tonsillar pillars with 2 per cent nupercaine solution and drops 2 to 3 cc. of a 5 per cent solution into the larynx. He reports no toxic symptoms in more than 2000 injections.

Balyeat and associates<sup>b</sup> give the patient a preliminary dose of adrenalin—in some cases, adrenalin and  $\frac{1}{8}$  grain of morphine if the patient is wheezing at the time the oil is to be given. They favor 1 per cent solution of cocaine hydrochloride

which, when the patient is asked to breathe deeply during the spraying, suffices to anesthetize the pharynx and trachea. In patients with very sensitive throats, they advocate the additional use of 10 per cent solution of cocaine to each subtonsillar region, which also abolishes the swallowing reflex.

A number of operators are able to instil the oil into the patient's larynx without any anesthesia at all, after a few times.

Ochsner,<sup>45</sup> Anderson,<sup>10</sup> Balyeat,<sup>8</sup> and Harris and Turkel,<sup>6</sup> after experimenting with several types of anesthesia, concluded that the application of 4 per cent solution of cocaine to the posterior wall of the pharynx, the base of the tongue, the uvula and the faucial pillars was simple and efficacious. For the larynx, a 10 per cent solution of cocaine was employed—in several cases directly to the larynx, by an applicator. In most instances, the spray was found satisfactory.

**Instrumentarium.**—The only two methods worthy of consideration are the bronchoscopic and the nonbronchoscopic. The former is of value in those cases where the irritability of the lower air passages is so great that oil injected by other methods is immediately expelled or not retained long enough to be of value. This method also permits introduction of the oil into a specially desired bronchus via a long catheter passed through the canal of the bronchoscope. The transcricoid needle method of injection, which I condemned shortly following its introduction for this purpose, I am happy to state has been abandoned. For the nonbronchoscopic means, a large choice of instruments are offered, mainly of two types: the syringe cannula and the bronchial catheter methods.

While a greater preference is shown to some form of cannulated syringe, because of its relatively easier adaptability to the average operator's manual dexterity, it can be readily demonstrated that the bronchial catheter, particularly the styletted type (Figs. 76, 77), possesses definite advantages that warrant its adoption for more general use. First, it permits the introduction of the tip of the catheter between the vocal cords under direct vision, and secondly, one is assured before injecting the oil that the catheter is definitely in the

trachea, thus assuring the operator that the oil is being injected into the bronchi and not into the stomach. Third, in bronchography, which is such an important preliminary procedure in the proper conduct of this treatment, the patient with the soft catheter between his lips can assume any position necessary to inject the oil into a particular bronchus with comfort, and permits the only satisfactory method of perform-

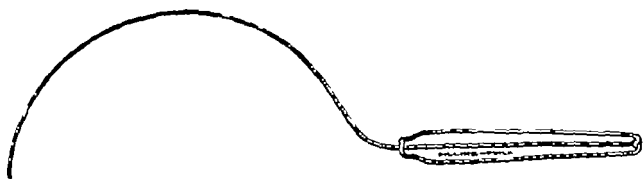


Fig. 76.—Stylet for author's tracheobronchial catheter.

ing bronchographic fluoroscopy. The tip of the catheter can be introduced to the openings of any of the primary or secondary bronchi while the patient is under the fluoroscope, either in the standing, oblique or horizontal postures, and it can be held in the trachea for prolonged periods of study, and varying amounts of the iodized oil can be injected into a number of desired bronchi at one sitting, either in one or both sides of

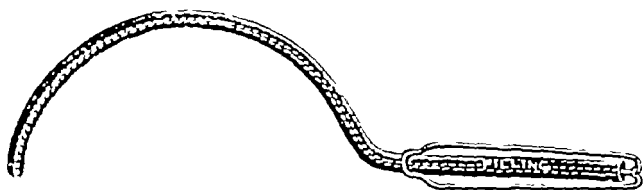


Fig. 77 -- Author's tracheobronchial catheter and stylet assembled.

the chest. Satisfactory results, however, can be obtained with one of the many forms of iodized oil syringes with attached cannula having a laryngeal curve. For this purpose the author in 1924 devised a well-balanced syringe (Fig. 78). It has a cannula with a flattened distal end, well-rounded to prevent irritation or damage to the vocal cords, and a slotlike opening permitting easy egress of the oil without using any force in

ejecting same. After preliminary anesthesia, gently hooking the end of cannula over the epiglottis, and permitting it to rest on the vocal cords, it will without any force, slip by its own weight between the cords into the trachea, when the oil can be gently expelled by gravity, drop by drop, into the desired bronchus. The use of this latter type is so well known that I will describe the styletted catheter method used in our intratracheal medication, as well as our method of preparation and anesthesia.

**Preparation of Patient for Treatment.**—In a well-considered routine it is most essential that a searching history, a careful physical examination, in most cases a preliminary roentgen chest examination and in some cases both roentgen and preliminary bronchoscopic examination, be undertaken.

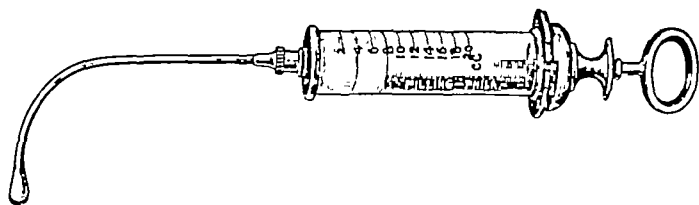


Fig. 78.—Author's iodized oil syringe.

Wassermann tests, sputum examinations and hematologic studies are all indicated at times.

Almost all writers agree that upper respiratory infection plays a large rôle in bronchial asthma. Thus roentgen and clinical examination of the paranasal sinuses are important. The association of nasal polyposis with a number of cases of asthma is recognized. The association of allergenic factors must be kept in mind even though certain writers, especially Anderson,<sup>10</sup> states that disregarding allergic elements he has had splendid results from iodized oil treatments alone.

Experience has shown that the early morning before breakfast is the best time, as, following a good night's rest, induced if necessary by a well-selected hypnotic, the patient's nerves are most quiet and it is easier to obtain his most helpful co-operation, in addition to which, the empty stomach avoids

nausea which occasionally interferes with smooth progress of the procedure. Postural drainage treatment is not necessary unless the case is complicated by bronchiectasis. In 1927<sup>47</sup> the author gave a complete résumé of this valuable adjunct to help relieve the lower air passages of excessive secretions.

The patient is permitted nothing after midnight preceding the morning of the treatment. Some cases may require a sedative such as a barbitol preparation an hour or two before the treatment. Certain extremely nervous types may even require a hypodermic of morphine a half to one hour before the treatment, much as one does preliminary to tonsillectomy under local anesthesia. Local anesthesia may be induced by one of the many means in vogue, the choice of either cocaine, nupercaine or similar drugs, as well as the method of application and the strength of the solution used being left to the operator. So-



Fig. 79—Author's pyriform sinus applicator for carrying anesthetic-soaked cotton.

lutions of cocaine vary from 2 to 10 per cent, and nupercaine from 1 to 3 per cent, according to the type of patient, as toleration to instrumentation of the throat varies greatly. Some patients do very well with a simple spraying of the throat and hypopharynx with 2 per cent cocaine solution, while irritable types may even require a preliminary hypodermic of morphine sulphate  $\frac{1}{4}$  grain with atrophine sulphate  $\frac{1}{150}$  grain in addition to a careful local swabbing of the throat and hypopharynx with 10 per cent solution of cocaine.

For general use, our routine is to apply a specially curved, cotton-tipped pyriform-sinus applicator which we devised (Fig. 79) moistened with freshly made 10 per cent cocaine solution, and to insert it in each pyriform sinus, first one side, and then the other. It should be held in position in each side from five to ten minutes, and after an interval of ten minutes, the pro-



cedure should be repeated. This is practically the same method utilized for local anesthesia preceding bronchoscopy. Inasmuch as this procedure requires the prolonged retention of the catheter in the tracheobronchial canal, it is best also to instill a few drops of warm 2 per cent cocaine solution upon the vocal cords as well as between them into the tracheal canal. The laryngotracheal cocaine syringe devised by the author (Fig. 80), has a curve particularly adapted for this procedure. After waiting a few minutes for the anesthetic to take effect, one is ready for the introduction of the tracheobronchial catheter. The wire stylet is anointed with sterile oil (such as olive oil, albolene or lipiodol) before slipping it into the catheter, to permit its easy withdrawal later, when the catheter is in situ. With the patient sitting in the usual position for laryngological

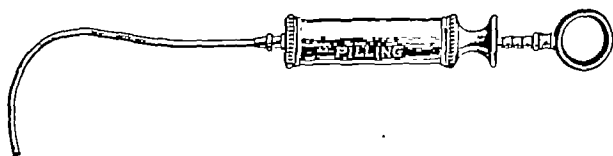


Fig. 80.—Author's laryngeal cocaine syringe for dropping anesthetic solution upon vocal cords and into trachea.

examination, and the laryngoscopic mirror in place, either the patient himself, or an assistant holds the extended tongue. Holding the patient's tongue in the proper position is, perhaps, the most difficult part of the entire procedure. To hold the laryngoscopic mirror in one hand and the handle of the stylet-catheter in the other while trying to insert its tip between the vocal cords of the patient with someone else endeavoring to hold the tongue in the proper position, either an assistant or the patient himself, is very difficult for a great number of physicians. So, in 1928,<sup>18</sup> I devised a special "finger-holder" for the laryngoscopic mirror which is admirably adapted for this purpose (Fig. 81). The tip of the stylet-catheter is inserted between the vocal cords while the patient is asked to take a deep inspiration. Before doing so, it is wise to explain to the patient that it is rarely possible to successfully intro-

duce the catheter at the first attempt so that he will not be too easily discouraged and to retain his cooperation. As soon as the instrument has passed several inches below the cords, immediately let go of his tongue and gently, with one hand fixing the position of the catheter at the upper teeth, and with the other grasping the proximal end (the handle) of the stylet, withdraw it.

The catheter is quickly and most gently slipped further down toward the carina of the trachea and the wire stylet withdrawn, the patient is told to firmly close his lips upon the catheter and to breathe slowly and regularly through his nose. If you fail upon your first attempt to pass the intratracheal catheter, or if in some patients it passes into the esophagus the

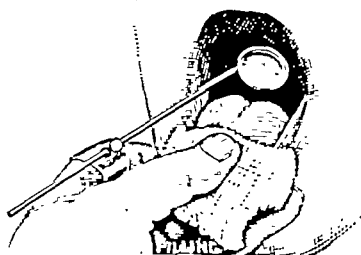


Fig. 81.—Author's finger-holder for laryngoscopic mirror.

first time it is essayed, simply withdraw it gently and wait a few moments before reintroducing it.

After the stylet is withdrawn from the catheter, tell the patient to fix the position of the instrument by compressing his lips firmly against it (not the teeth). Then, to be certain that the catheter is properly placed in the trachea, if the proximal end of the catheter is put close to the operator's ear, one can hear the patient breathing through the tube. Then, connecting the previously filled syringe with the required amount of warmed iodized oil, one can inject the oil slowly and with certainty into the desired bronchus, according to the posture the patient is told to assume. For the first injection, bronchographic fluoroscopy is always done, immediately followed by a roentgen study of such films as the individual case may require.

**Previous Types of Treatments.**—Anderson<sup>10</sup> states that many of his 360 cases treated with iodized oil had previously been treated with all the conventional treatments with little or no results. No other treatment was given by him excepting occasional use of adrenalin for the immediate relief of an attack. Balyeat<sup>8</sup> reports that most of his cases were of the intractable type and poor results were obtained in many of these patients by the usual methods of treatment.

Penta<sup>9</sup> states that his experience showed that patients over thirty years of age who are suffering from bronchial asthma will not be benefited by any form of allergenic treatment.

**Frequency and Intervals of Injections.**—Penta<sup>9</sup> instills 20 cc. every week for a period of two months, then gradually increases intervals (depending on course of individual case). Most cases at end of fourth month get oil once a month.

Anderson<sup>10</sup> injects 20 cc. into the lower lobe bronchus of one side and one week later, providing no untoward reaction follows the first injection, follows with a second similar injection into the lower lobe of the opposite side. He advises frequent fluoroscopies to guard against overloading the alveoli with oil. Never more than 50 per cent of the vital capacity should be reduced. It may increase frequency of attacks and produce cyanosis. If after several injections in lower lobes no improvement follows, then follow same procedure in middle and lower lobes. When improvement is noted, gradually reduce amount of oil and increase interval of treatments. When attacks cease for 6 months, cease treatments until recurrence, and then renew injections.

Balyeat<sup>8</sup> and associates first instil 20 cc. in one side, take a roentgen film, and the next day repeat the procedure on the other side. If case is treated, 10 cc. of oil are given on each side about four days later, from then on once a week. After a number of injections have been given, the interval is increased to a two-, three-, or four-week interval, or even longer, according to the individual needs of the case. In establishing their routine, they tried various intervals, but found weekly intervals sufficed.

Harris and Turkel<sup>6</sup> administer 20 cc. of the iodized oil weekly until definite improvement is noted, then every two weeks, until further improvement, when the interval is increased to one month. When no improvement was noted after six weekly injections, treatment was discontinued and resumed six months later.

**Reaction Following Injection.**—The oil is well tolerated in most patients. In some a convulsive cough may result lasting from half an hour to several hours. It may be mild, very severe, or even produce a violent asthmatic paroxysm. As little as 2 cc. may cause this. In others too rapid injection of the oil may cause dyspnea or even acute collapse of the lung.

Some asthmatics with a complicating chronic laryngitis, tracheitis, or bronchitis have an easily excitable cough reflex, and as soon as the oil contacts the mucosa, it is expelled by a severe coughing paroxysm.

A chill, rise of temperature, increased pulse rate and pain in the injected area may occur in some cases. Acute iodism occurred in only one of our cases. It followed the first injection of a female of eighteen, causing a transient though enormous swelling of the thyroid.

It occurred in 8 of Anderson's 360 cases, and being susceptible to iodism, the treatment was discontinued. No chronic iodism occurred even in cases where large aggregate amounts were injected over long periods.

There were 8 cases of pneumonia in this group. Five of bronchopneumonia; four of these recovered and one died. Three were lobar pneumonia in aged individuals, all of whom recovered. x-Ray examination of the seven who recovered showed considerable oil in the lungs. Treatment in four of them was continued for months without recurrence of pneumonia.

In our 114 cases, 1 case of transient bronchopneumonia followed the third injection. This patient, female, thirty-four years old, recovered in a few days without any special treatment. We believe this was due to the fact that the patient

was in the initial stage of a grippal infection and therefore we thereafter refused to inject any patients suspected of developing a fresh cold or already advanced in the early stages of an acute nasobronchial infection.

*Precaution.*—If the iodized oil is accidentally injected into the patient's stomach, remove at once via the stomach tube and give a brisk cathartic.

*Fatalities.*—The possible dangers of iodism from the use of iodized oil has already been reported by Firth,<sup>48</sup> Carmichael<sup>49</sup> and Eller,<sup>50</sup> and other untoward effects following the injection of iodized oil into humans were well presented in 1932 in the Journal of the American Medical Association.<sup>51</sup>

The first death, however, directly attributable to the injection of iodized oil was reported by Macdonald in 1932.<sup>52</sup> In this case death followed the injection of 20 cc. of iodized oil. The fatality was considered due to the patient's sensitiveness to iodine. The second death directly attributable to the intrabronchial instillation of iodized oil was recently published in the Journal of the American Medical Association by Goldstein.<sup>53</sup> A male patient of forty-three years received a lung injection of 20 cc. of iodized oil for diagnosis. Films showed no bronchiectasis. Next day a papulopustular eruption appeared on his face, then spread to chest, arms and hands, and following nausea, the patient became stuporous from a severe toxemia. The oral mucosa showed vesicobullous lesions. Urinalysis revealed an acute glomerulonephritis. In spite of treatment, the iododermatous lesions spread over most of the body and the nephritis became more marked and death ensued twenty-six days after the onset.

He concluded that despite the negligible absorption of iodine by the bronchial mucosa, it is entirely conceivable that in a markedly sensitive or allergic individual a sufficient quantity could have been absorbed to be responsible for the eruption and that death ensued as a result of a nephritis plus an overwhelming toxemia.

*Cases Unrelieved by Iodized Oil.*—It is instructive to study some of the cases unrelieved by the type of treatment

under consideration. Poor or no results obtained in cases complicated with healed tuberculosis, advanced emphysema, pneumoconiosis, myocarditis and bronchiolar obliteration following irritating gaseous inhalations.

In 3 of our cases, malignancy was found among the asthmatics referred to us in this series, two bronchogenic and one metastatic. These, of course, were not treated. Penta<sup>9</sup> stated that during the past year, 1936, 14 cases of bronchial carcinoma were found that had been previously diagnosed and treated for bronchial asthma. He well calls attention to the fact that bronchoscopy may be the means of ruling out intra-bronchial pathology, which may be the underlying cause of the asthmatic paroxysms. Two cases of severe asthma in adults associated with attacks of massive lung collapse were unrelieved by iodized oil injections, but following bronchoscopic-suction removal of large, tenacious masses of mucus from lower main lobe bronchi, followed by resumption of the iodized oil injections, were greatly aided as to frequency and severity of attacks.

Four cases unrelieved by the injections over a long period were cured after determining unsuspected allergic irritants and being desensitized to same. One case of papilloma of the right lower lobe bronchus was eventually discovered in a case receiving the injections without relief. Upon bronchoscopic removal, almost immediate cure was obtained. One case not obtaining relief after eight months' treatment with the oil was rechecked. Roentgen study revealed posttracheal pressure from a retrotracheal extension of an enlarged accessory thyroid lobe. Surgical removal of this mass was also immediately curative. One case of luetic infiltration of the peribronchial tissues (tertiary syphilis) was diagnosed after a prolonged course of iodized oil which was of no avail in relieving the symptoms of asthma. Following an intensive antisiphilitic treatment with salvarsan and iodides, this patient was markedly improved. One case in a boy of ten years with typical asthmatic seizures, after no relief with the oil, was found by roentgen and bronchoscopic study to have a small piece of peanut shell lodged in the

opening of the main left upper lobe bronchus, following removal of which attacks promptly ceased.

All of the above cases are from the records of the earliest cases treated in this series in which the presence of asthmatic seizures was considered evidence of bronchial asthma and immediately were placed on the iodized oil treatment.

This but adds to the proof of Jackson's<sup>54</sup> dictum that "*All is not asthma that wheezes.*" Our earlier experiences lead us to a more serious consideration of the etiological factors in the cases sent to us for treatment and to realize that of course the use of iodized oil in such cases will prove of little or no value.

Thus, in a given series of cases, if certain patients do not respond after receiving the oil for a reasonable length of time, it is advisable to recheck the case by clinical, roentgen and laboratory methods.

#### **Other Respiratory Pathology Accompanying Asthma.**

—Aside from the well-known upper respiratory pathology so frequently associated with and considered of etiologic significance in bronchial asthma such as paranasal sinusitis and nasal polyposis, the other bronchopulmonary lesions accompanying asthma consisted chiefly of laryngitis, tracheitis, tracheobronchitis, emphysema, and bronchiectasis. Pulmonary tuberculosis and cases of suppurative pulmonary disease were nil in all of the reports by the various authors quoted in this article. The few cases of hemoptysis noted were considered due to the bronchiectasis.

The chief chest pathology noted, other than that related to the lungs, in the more serious and protracted types of asthmatics is that referable to the cardiovascular system. With advanced myocardial degeneration and its frequent accompaniment, pulmonary edema, particularly at the bases of the lungs posteriorly, one must seriously consider the still further embarrassment of cardiorespiratory function which might result from the indiscriminate injection of iodized oil in already damaged tissues.

Bronchiectasis was present in over 30 per cent of these

combined groups. This was undoubtedly due to the fact that by far the greater proportion of the cases treated were of the chronic intractable type. This was proved by bronchography. The bronchiectasis was of three types, cylindrical, saccular, and mixed or combined types. Most of the cases of asthma, however, were found to be associated with the cylindrical type, involving usually both lower lobes in the chronic type, almost always the lower right lobe; although any one or almost any combination of two or more lobes could be found.

Emphysema was found in over 20 per cent of the cases studied, more marked in the cases of longer duration, and generally bilateral. Foreign bodies were found in the course of preliminary bronchoscopic examination in 9 cases, removal of which immediately was followed by relief of the asthmatic seizures, except in 1 case where marked pulmonary suppuration had already occurred.

Several authors, Anderson<sup>10</sup> and Penta,<sup>9</sup> noted the presence of a marked laryngitis, tracheitis, or bronchitis. Penta<sup>9</sup> was struck with the frequency and severity of the tracheobronchitis found during bronchoscopic examination of 75 asthmatics.

Steinburg,<sup>55</sup> Anderson<sup>10</sup> and myself believe that there is a direct relation between the frequency of the attacks and "the number of plugged tubes" (extent of bronchial obstruction by excessive, viscous secretion).

**Summary.**—A survey of 1000 cases of asthma of various types reported by eighty-four different observers in various parts of the country, revealed the following facts:

The ages ranged from eight years to eighty-one years.

The duration of the disease varied from two months to fifty-one years.

The average duration of treatment, four months.

The minimum number of treatments needed to relieve was 1 (in 11 cases).

The maximum number of treatments needed to relieve was 80.

The average number of treatments needed to relieve was 32.



The percentage of cases completely relieved was 24 per cent.

The percentage of cases markedly relieved was 34 per cent.

The percentage of cases slightly relieved was 17 per cent.

The percentage of cases not influenced by this method was 25 per cent.

The number of deaths attributable to injection of iodized oil into the lower air passages and reported in the literature were two.

Considering that this series represents nearly 35,000 individual injections of iodized oil, it may be concluded that in the average well-studied case the method is relatively innocuous, but that while serious reactions are comparatively uncommon and fatalities very rare, one must bear in mind the possibilities of same.

With few exceptions, the history of every patient showed an inherited asthmatic background (Anderson<sup>10</sup>).

**Conclusions.**—The direct intratracheal injection of iodized oil offers an additional aid in the treatment of bronchial asthma. It is not a panacea. It is not possible to predetermine what types of cases so treated will be aided, nor what percentage will be symptomatically cured. A gratifying number of patients were absolutely relieved for periods varying from three to seven years; this freedom from the paroxysms equaling, if not surpassing, the length of time obtained by treatment with any other means.

Many of all types of cases that have resisted all other forms of treatment have been completely relieved for prolonged periods, including the allergic as well as the nonallergic types.

Other forms of therapy of proved value in the treatment of asthma must not be disregarded, particularly in those cases in which the use of iodized oil has proved unsuccessful, and vice versa, in cases in which any of the usual methods have been ineffective, the use of iodized oil may prove of signal value. The percentage of successful results seems to depend upon the particular preliminary study of the patients, eliminating those with gross bronchopulmonary pathology, as well as a careful

check-up from time to time by both clinical and roentgen study. In cases not responding after some months of repeated consecutive injections, it is well occasionally to withhold the treatments for periods of from one to even six months, and to then resume the previous routine. The main keynote to success with this method is to individualize each patient and treat him accordingly.

While the beneficial results following the treatment of bronchial asthma by intratracheal injections of iodized oil has been known for over ten years, and encouraging reports continue to appear in the literature, much more research remains to be done, and a consideration of the ultimate results obtained in some thousands of cases considered permanently relieved, one may arbitrarily say, five to ten years after cessation of treatment. As a palliative measure, and occasionally giving startling results, it is a splendid addition to our present limited therapeutic armamentarium for the treatment of bronchial asthma.

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Other forms of therapy of proved value in the treatment of asthma must not be disregarded, particularly in those cases in which the use of iodized oil has proved unsuccessful, and vice versa, in cases in which any of the usual methods have been ineffective, the use of iodized oil may prove of signal value. The percentage of successful results seems to depend upon the particular preliminary study of the patients, eliminating those with gross bronchopulmonary pathology, as well as a careful

check-up from time to time by both clinical and roentgen study. In cases not responding after some months of repeated consecutive injections, it is well occasionally to withhold the treatments for periods of from one to even six months, and to then resume the previous routine. The main keynote to success with this method is to individualize each patient and treat him accordingly.

While the beneficial results following the treatment of bronchial asthma by intratracheal injections of iodized oil has been known for over ten years, and encouraging reports continue to appear in the literature, much more research remains to be done, and a consideration of the ultimate results obtained in some thousands of cases considered permanently relieved, one may arbitrarily say, five to ten years after cessation of treatment. As a palliative measure, and occasionally giving startling results, it is a splendid addition to our present limited therapeutic armamentarium for the treatment of bronchial asthma.

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### MANAGEMENT OF NUTRITIONAL ANEMIA IN INFANCY

THE successful management of nutritional anemia in the infant should be directed toward the prevention of the iron deficiency which constitutes its cardinal feature. The prophylaxis of this condition includes supervision of the prenatal period with respect to the prevention and treatment of hypochromic anemia in the mother. Corrigan and Strauss<sup>1</sup> recently reported that this condition could be largely obviated in the mother by the administration of iron during the last four months of pregnancy and it seems entirely reasonable that additions to the prenatal stores of iron may be affected by this means.

With the birth of the infant many procedures have been employed to prevent the abnormal hemoglobin levels that may follow the termination of the period of adjustment. These endeavors are of particular moment with the premature, twin or immature infant, in whom hemoglobin values reach excessively low levels. Prophylaxis of anemia in normal infants was successfully carried out by Helen Mackay<sup>2</sup> with the routine use of dried milk containing a supplement of iron and ammonium citrate. This has also been accomplished in prematures by Abt and Nagel<sup>3</sup> with a combination of the secondary anemia liver fraction and iron, and by Merritt and Davidson<sup>4</sup> with iron; in both studies the additions were instituted between two and three weeks of life.



**The Hemoglobin Determination.**—The problem of prophylaxis as well as that of treatment involves an inherent difficulty which arises from the lack of data as to optimum hemoglobin value which will promote the greatest growth and development of the infant. This difficulty is illustrated by the observations of Elvehjem<sup>5</sup> and his associates who were able to raise the hemoglobin level of infants to values from 12 to 13.5 Gm. per 100 cc. of blood by the addition to their diets of ferric pyrophosphate and copper. In a previous study they had noted values between 11 and 12 Gm. in a group of normal untreated infants from six months to two and one-half years of age. Although the higher hemoglobin content appears desirable, the value for best health has not yet been established. Closely controlled observations would be necessary to determine the advantages of the elevated hemoglobin in the former group over the latter with respect to morbidity, mortality incidence and growth increments.

In the absence of this knowledge, a hemoglobin determination in an infant should be compared with a range of values obtained with infants whose physical development measures up to normal standards. The range of values between 10 and 12 Gm. of hemoglobin per 100 cc. of blood is suggested as a basis of comparison for normal infants from two months of age to the end of infancy, figures already found suitable for patients in the hospital as well as in private practice.

It is at once evident that for routine use, the hemoglobin determination of the blood of an infant must depend upon a simple yet reliable method. Of these, a colorimetric method depending upon the production of acid hematin fulfills these requirements. The Newcomer method, utilizing standardized color disks in a colorimeter, may be used for comparison; or an even simpler method embodies some of the principles of the Sahli method with modifications to increase its precision. This simple method is highly satisfactory if caution is exercised as to the use of standardized nonfading solutions for comparison, as well as an accurately graduated tube and pipette.<sup>6</sup>

For many years I have been using a modified Sahli hemoglobinometer (Hellige type), in which, after dilution of the blood sample, the hemoglobin is read directly in grams from graduations on the tube. With this method, 0.02 cc. of blood from the finger is mixed with the customary 0.1N HCl reaching to the mark 10 on the graduated tube. Placing the tube containing the mixture in hot water ( $55^{\circ}$ – $60^{\circ}$  C.) for seven minutes has been suggested<sup>9</sup> as a method to expedite the endpoint. As an alternative, dilution may be postponed for a period of at least twenty minutes to one hour at room temperature. After the maximum color has developed, dilution is carried out carefully with distilled water until the color of the standard is matched. This type of apparatus employs standard nonfading prisms, each one of which is fixed at either side of the tube containing the diluted acid hematin solution in a housing resembling that of the Sahli hemometer. In this type the hemoglobin is expressed as grams per 100 cc. of blood, the standard for 100 per cent being designated as 14.5 Gm. of hemoglobin. It is important to emphasize that it is confusing and unnecessary to compare values obtained for infants with this adult figure. If facilities are available, it is advisable to check this instrument periodically with the oxygen capacity or iron methods, in order to determine whether fading of the standards has occurred. The simplest procedure, therefore, is to express the hemoglobin value as grams per 100 cc. of blood by direct reading from the hemoglobinometer tube and to report it together with the number of grams of hemoglobin normal for the particular age period.

The values for normal infants from the age of two months, the time at which usually the lowest level is reached following birth, remains fairly constant. The range from two months to the end of the first year, according to four recent American studies<sup>7, 8, 9, 10</sup> of hemoglobin value which are significant because of their close correspondence, is approximately from 10 to 12 Gm. of hemoglobin per 100 cc. of blood, values which are maintained during the second year of life as well. The value of 10 Gm. of hemoglobin may be designated as the

lower limit of normal. Strictly speaking this is an arbitrary figure since it is not unusual to encounter infants, particularly prematures or twins, who are normal in every respect but whose hemoglobin after the second month falls somewhat below this value. In the main, however, the full-term infant of average birth weight whose supervision is placed under the care of the private physician possesses an average hemoglobin content of 11 Gm. or more. The infant whose hemoglobin persistently falls below 10 Gm. on repeated examinations during the first third of infancy requires careful dietary regulation in the subsequent period, often in conjunction with specific anti-anemic therapy.

The clinical appearance of an infant often proves an unreliable index of anemia since pallor may depend upon qualities of the skin such as its texture, racial and familial characteristics, and upon transitory changes in the caliber of the blood vessels.

Whereas with the premature and twin, tests for hemoglobin content should be begun during the second month of life, with the normal full-term infant these may be postponed until the end of the second or third month.

By following closely infants whose hemoglobin content fluctuates about the level of 10 Gm. per 100 cc. of blood, carrying out tests at frequent intervals and instituting anti-anemic therapy if the same or lower values are consistently obtained, treatment is confined to infants in whom the development of iron deficiency becomes apparent and obviates the necessity for routine iron administration to all infants. Particular attention to the hemoglobin level should also be directed to all infants who are growing rapidly; to those who are troubled by frequent infections, even of minor severity; to those whose mothers, during the latter part of pregnancy, were known to have exhibited a profound anemia; and to infants who, during the neonatal period, were suffering from a blood dyscrasia such as primary anemia of the newborn or who have survived the condition of icterus gravis. Infection may result in serious iron deficiencies, manifested not alone

by a diminution in the hemoglobin content but by a decrease in the numbers of erythrocytes and by pronounced changes in their morphologic appearance. Iron therapy is unsatisfactory during the acute stage of the infection, but is effectual during convalescence.

**Iron Requirement.**—The amount of iron necessary to satisfy the infant's daily requirements has been determined, as in older age groups, by balance studies. Although the iron requirement of the infant has been stated to range as low as 1 to 2 mg. per day,<sup>11</sup> even this quantity may be difficult to obtain during the period when milk constitutes the sole article of diet. For preschool children, it has been demonstrated that 0.6 mg. per kilogram of body weight is sufficient for maintenance and growth. The difficulties of absorbing iron from the intestine, and its presence in food partly in a form not available for hemoglobin formation necessitate that infant values at least approximate those of older children. In the final analysis, the simplest index of an adequate iron intake can only be obtained by repeated hemoglobin examinations.

**Inorganic Iron Preparations.**—With the repeated observation in a specific instance that the hemoglobin fluctuates about the lower range of normal and that at times drops below it, there is a clear-cut indication for iron administration. When this condition exists as well in the older infant who is on mixed feeding, medicinal treatment should likewise be instituted since the results are more rapid. Organic iron preparations are unsuitable for hemoglobin synthesis, whereas the experience of recent years has repeatedly confirmed the striking results with inorganic iron. The choice of an inorganic preparation for the infant, as for the adult, depends upon its acknowledged activity, ease of administration, tolerance, inexpensiveness and solubility. The latter consideration applies particularly to the infant since inorganic salts that are readily ingested by the adult may be unsuitable for the infant. The absorption of iron from the intestine of the infant is subject to a variety of influences; in part similar to those of the adult and in part

resulting from local conditions incident to its own stage of development. The dosage of iron to be administered depends, therefore, on these considerations, so that a specific amount cannot be definitely assigned for a particular age. The dosage should be controlled by frequent hemoglobin estimations, noting at the same time tolerance of the infant for the preparation employed. The dosage of iron must be considered in relation to the iron content of the salt prescribed; these differences being illustrated in the following list of commonly used preparations:

Reduced iron, U.S.P., contains not less than 90 per cent metallic Fe.

Ferrous sulphate, U.S.P., contains not less than 20 per cent Fe.

Ferrous lactate, N.F., contains not less than 19.36 per cent Fe.

Saccharated ferrous carbonate, U.S.P., not less than 15 per cent ferrous carbonate (equivalent to approximately 7.5 per cent iron).

Iron and ammonium citrate, U.S.P., brown scales, contains not less than 16.18 per cent Fe.; green scales, not less than 14.5 per cent Fe.

Ferric pyrophosphate, N.F., soluble scales, contains not less than 10.5 per cent Fe.

Ferric chloride, U.S.P., not less than 20 per cent Fe.

Ferric glycerophosphate, N.F., not less than 17 per cent Fe.

Table 1 gives a partial list of the preparations and their dosage as mentioned in the recent literature.

The choice of an iron salt may be confusing unless it is remembered that whatever inorganic salt of iron is employed, satisfactory results can be obtained with it provided it is prescribed in adequate dosage. With the infant, however, the salt should be preferably soluble so that it may be administered in water, milk or a fruit juice. Reduced iron and saccharated ferrous carbonate possess the disadvantage of requiring suspension because of their insolubility. In recent years iron

TABLE 1  
PREPARATIONS AND DOSAGE OF VARIOUS IRON SALTS USED RECENTLY IN NUTRITIONAL ANEMIA OF INFANCY

Iron preparation.	Dosage.	Reference.
1. Iron and ammonium citrate in 10 per cent solution supplemented by 0.5 per cent solution of copper sulphate.	2 cc. of the iron and 1 cc. of the copper solution per kilogram of body weight daily.	Josephs. <sup>12</sup>
2. Iron and ammonium citrate incorporated in milk, supplemented in some cases by the feeding of extra iron.	4.5 to 9 grains daily, to maximum of 15 grains.	Mackay. <sup>3</sup>
3. Saccharated ferrous carbonate.	30 to 60 grains daily.	Bass and Denzer. <sup>13</sup>
4. (a) Iron and ammonium citrate. (b) Ferrous sulphate.	Infants 1 to 2 Gm. daily. Children 4 to 6 Gm. daily in sweetened orange juice or water. Infants 6 to 8 grains daily. Children 10 to 12 grains daily.	Blackfan and Diamond <sup>14</sup>
5. Ferric pyrophosphate (10 Gm. are dissolved in 250 cc. of distilled water containing 5 per cent alcohol together with 0.2 Gm. of copper sulphate).	1 teaspoonful given daily. This dose contains 25 mg. of elemental iron and 1 mg. of elemental copper.	Elvehjem, Siemers, and Mendenhall. <sup>5</sup>
6. Iron and ammonium citrate in 50 per cent aqueous solution.	0.3 Gm. of the salt per kilogram of body weight to premature infants to prevent anemia.	Merritt and Davidson. <sup>4</sup>
7. Ferric glycerophosphate.	Administered in solution: 10 to 21 grains daily, supplemented in some cases by $\frac{1}{4}$ to $\frac{1}{2}$ grain of copper sulphate.	Usher, MacDermot, and Lozinski. <sup>9</sup>
8. Ferrous sulphate dissolved in glucose solution.	12 grains daily in divided doses.	Parsens and Hawksley. <sup>15</sup>

and ammonium citrate has enjoyed deserving popularity since widespread usage has confirmed its effectiveness, while its solubility and ease of administration have rendered it especially attractive for infant medication. Iron and ammonium citrate is commonly prescribed in stock solution form usually in a strength of 10 per cent. While this is satisfactory, my practice has been to employ the powdered scales, a small dose of only 5 grains being offered at the start. With the assurance that the medication is well tolerated, the amount is gradually increased. Sweetened solutions of iron kept for any length of time require alcohol as a preservative. When the salt is dispensed in capsules, they are opened before feeding and the contents dissolved in the bottle or glass of milk; or water or sweetened orange juice may be used as vehicles. At times during treatment vomiting, constipation or diarrhea follow the use of the salt, especially if the dose is suddenly increased. Should these untoward symptoms appear, the quantity of iron may be temporarily reduced, following which it may be gradually stepped up to the level necessary to promote hemoglobin regeneration. I have found that in some instances gastric irritation could be related to the fact that the scales of iron and ammonium citrate were not thoroughly pulverized. In the event this cannot be satisfactorily accomplished, reliable proprietary preparations are available in capsule form, each containing 7 to  $7\frac{1}{2}$  grains of the salt. In the infant with nutritional anemia of a moderate grade the desired hemoglobin level can be obtained usually with a daily dose approximating 1 grain of iron and ammonium citrate per pound of body weight, totaling 15 to 30 grains. With severe cases in older infants 45 grains and more are at times required, and it is surprising how well these amounts are tolerated. It may be desirable, however, when the dosage appears excessive, either to supplement the iron with traces of copper or to replace the iron and ammonium citrate with another salt, particularly if refusal is encountered.

As already stated, although there is seldom a copper deficiency in hypochromic anemia, instances of nutritional anemia

in infants have been recorded in which the introduction of minute traces of copper to the iron salt resulted in prompt acceleration of hemoglobin production from a previously stationary level. Although the same results may have been accomplished by substituting another iron salt or still further increasing the quantity of the original preparation, the introduction of a small copper supplement should be kept in mind when simple nutritional anemia becomes refractory.

Iron and ammonium citrate may be dispensed with copper sulphate in solution form as follows:

Iron and ammonium citrate	5.0 Gm.
Copper sulphate	0.06 Gm.
Simple syrup to make	60.0 cc.

One teaspoonful of this solution contains approximately 5 grains of the iron salt and  $\frac{1}{15}$  grain of copper sulphate corresponding to about 20 mg. of metallic iron and 1 mg. of copper respectively. Recently Fantus<sup>16</sup> has pointed out that syrup of cinnamon of the Sixth National Formulary constitutes an excellent vehicle for iron and ammonium citrate. With the same quantity of the vehicle the iron salt may further be increased to twice or three times in strength (10 Gm. to 15 Gm.) while the dosage of copper remains unchanged. Three teaspoonfuls daily of the largest amount (15 Gm. of iron and ammonium citrate in 60 cc. of the vehicle) prescribed for the infant contains approximately 45 grains of the iron salt and the  $\frac{1}{5}$  grain of copper sulphate. The utilization of iron is subject to so many individual factors, however, that an exact dosage cannot be stated but must depend upon repeated hemoglobin estimations.

Although with careful regulation of dosage, ferric ammonium citrate has fulfilled the requirements of a reliable iron salt for the cure of nutritional anemia, recent studies have emphasized the advantages of ferrous compounds. The claims for the latter are based on experimental observations, showing that iron in only the ferrous state is absorbed from the gastro-



intestinal tract and that the potency of any iron salt depends upon the degree to which free ferrous ions are liberated following its ingestion. The greater utilization of iron, as derived from the ferrous salts for hemoglobin formation in hypochromic anemia, has been demonstrated by Witts.<sup>17</sup>

Of the ferrous salts, the sulphate has generally been chosen for clinical use—its superiority supposedly resting upon the activity of its ferrous ions and upon the smaller dosage required to secure a therapeutic result as compared with the more complex ferric salts heretofore employed. Its solubility makes it preferable to its earlier bivalent predecessor, saccharated ferrous carbonate. Clinical trial at the hands of many clinicians has already attested to the advantages of the ferrous iron, principally because the hemoglobin level is raised with smaller doses.

It has been pointed out by Parsons and Hawksley<sup>15</sup> that ferrous salts in solution tend to be converted to the ferric form. To prevent oxidation they recommend, as a suitable vehicle for ferrous sulphate, a syrup made by dissolving glucose in water. These authors noted a favorable response in a few infants with only 12 grains daily. Practically, the administration three times daily of a teaspoonful of a solution of 4 Gm. of ferrous sulphate in 60 cc. of glucose solution would assure this intake, although actual dosage can be determined only by progress of the anemia. While the exact strength of the glucose solution required to prevent oxidation is not known, it appears that a concentration above 25 per cent is essential. The ease with which ferrous sulphate undergoes oxidation indicates that its efficacy may depend upon other properties than its supposed ready yield of ferrous ions. Small quantities of this medication should be ordered, otherwise a preservative is necessary. *Powdered ferrous sulphate* may also be dispensed in 3- or 4-grain capsules and administered according to the suggestions mentioned for iron and ammonium citrate. To assure maintenance of its ferrous state, relatively few capsules should be kept on hand at any one time.

In the main, ferrous sulphate has been employed in adults

with hypochromic anemia and there is no reason to expect that it cannot be employed with similar satisfaction in the treatment of nutritional anemia of infancy. Actually the ideal iron preparation for use in infancy has not yet been determined. The most favorable results are obtained by the exercise of skill in the administration of one of the inorganic salts whose activity has been proved by clinical trial.

**Diet.**—The diminished iron content of milk has led to the suggestion that it be mineralized with iron and copper preliminary to distribution. The milk employed by Mackay,<sup>2</sup> in which iron and ammonium citrate had been incorporated, served effectively as a prophylactic agent against nutritional anemia. With the means available of detecting the earliest signs of a diminished hemoglobin concentration and the prompt institution of antianemic therapy, this procedure appears unnecessary. The majority of infants, whose diet is adequately supervised and who are free from infection, maintain a level of hemoglobin production well within the normal range. The reason for this probably rests with the earlier introduction of a mixed dietary characteristic of present-day pediatric practice.

Prolonged lactation or an exclusive diet of milk constitutes the outstanding cause of nutritional anemia. Refusal of solid food persisting through the latter half of the first and during the second year of life, has often been productive of such severe anemias that transfusion becomes necessary. At times, the parent or nurse is at fault in that too much reliance is placed upon the conception that milk constitutes a complete food, so that the intelligent persistence in offering solid food is neglected.

Nutritional anemia produced in the infant in this manner is comparable to that of the young experimental animal who is maintained on an exclusive milk diet. The iron from prenatal stores and that derived from blood destruction in the neonatal period vary quantitatively to such a degree with the individual infant that it is impossible to foretell exactly when the introduction of solid food becomes essential. When the blood examination reveals a diminishing hemoglobin content

in an infant after six months, who is refusing solid food, the ingestion of milk requires curtailment. It is at times necessary to reduce the milk intake drastically before solid food is taken by the infant. It should be remembered, however, that the most important factor in the rapid correction of the anemia consists in the administration of medicinal iron in adequate dosage simultaneously with diet changes.

The addition of cereals to the diet between three and four months of age contributes little to the mineral requirements of the infant. With the exception of oatmeal and whole wheat, cereals are notably deficient in iron, since the process of milling deprives the grain of its germ and the outer layers in which this mineral is held. A special cereal mixture\* has been devised by Tisdall, Drake and Brown<sup>18</sup> which contains the vitamins and mineral elements including iron in appreciable amounts. While feeding this cereal in the treatment of anemia in the experimental animal has led to contradictory results,<sup>19, 20</sup> an elevation of hemoglobin was noted when it was included in the diet of older infants and children. Since a primary object in the prevention of nutritional anemia consists in the choice of foodstuffs rich in iron, this special cereal mixture deserves clinical trial to determine its suitability for restoring the diminishing iron reserves of the infant.

Vegetables introduced in the dietary of the infant at about the fifth month serve in a great measure as a source of the constituents essential for hemoglobin synthesis. As already stated, hemoglobin consists of a protein, globin and of hematin; the latter consisting of iron in association with four pyrrole groups. While safeguarding the daily iron intake by the young infant against depletion of iron reserves is undoubtedly accomplished by the adequate intake of vegetables, it is probable that the latter constitute a source of other factors required for promoting blood formation. A recent study by Patek<sup>21</sup> indicates that the human body can use preformed pyrrole sub-

\* This is manufactured by Mead Johnson & Company and is known as Mead's Cereal, and in its dried and precooked form as pabulum.

stances, as derived from chlorophyll, for the building of hemoglobin. It is interesting, however, that in nutritional anemia of infancy there appears to be no deficiency in the organic factors as represented by amino-acids and pyrrole substances, since the blood responds rapidly to the addition of sufficient inorganic iron alone. Our knowledge in this respect, however, is still incomplete and the early feeding of vegetables may also serve as a means of restoring diminishing reserves of organic elements.

Solid foods are introduced in the diet of the young infant sooner than formerly, so that cereals are now commonly added at the third month, puréed vegetables, fruits and egg between the fifth and seventh months, and meat by the tenth month. With the realization that this program is empirical and in the endeavor to supply the infant with additional sources of the necessary vitamins and minerals as soon as possible, some of these foods, such as egg, have been included by practitioners at even earlier periods. In recent studies by Schlutz<sup>22, 23</sup> of the iron metabolism of normal infants who had been fed spinach in addition to the milk formula from the age of five weeks, no beneficial effect was noted upon the iron retention. The diminished secretion of gastric juice in many young infants doubtless influences the impaired absorption of iron despite the most zealous efforts to prepare vegetables properly for infant consumption.

From the classification by Stiebeling<sup>24</sup> of a large variety of fruits and vegetables according to their iron content, the following list has been prepared to apply more especially to the period of infancy. Obviously, relatively few of the foods enumerated are adapted for the infant of five months when vegetables are started, but with increasing age and development they can be gradually incorporated in the diet. It is also apparent that many of these foods cannot be consumed in sufficient quantity to satisfy the iron requirement, but they can contribute to it in part when included in the more extensive dietary assortment offered the older infant.

The iron content of the foods in this list is based on the

TABLE 2  
IRON CONTENT OF VEGETABLES AND FRUITS  
(After Stiebeling<sup>24</sup>)

EXCELLENT (0.00160 per cent or more)	GOOD (0.00080 to 0.00159 per cent)	FAIR (0.0004 to 0.00079 per cent)
Beans, lima Beet tops Chard Dandelion greens Kale Parsley Peas, English garden Spinach Turnip tops Water cress	Artichokes Asparagus Beans, green string Beets Broccoli, sprouting Cauliflower Escarole Green lettuce Potatoes  Blackberries Blueberries Raspberries	Apricots Avocados Bananas Beans, yellow wax Cabbage Carrots Celery, stalk Mushrooms Okra Onions Oranges Parsnips Rhubarb Squash, winter Strawberries Tomatoes Turnips

analysis of the edible portions as prepared for table use. The lack of conformity of iron values, as noted in the determinations of a number of investigators, arises from the multiplicity of methods employed, the preparation of the specimens before analysis and natural variations in the moisture and iron content of different samples of the same food material. In addition to the foods stated, prunes, dates, wheat bran and lentils have been pointed out by other observers as possessing a high iron content.

Of the foods observed by Whipple and his associates<sup>25, 26</sup> to be potent for hemoglobin regeneration in the experimental anemia of dogs produced by bleeding, liver surpassed all others, beef, calf, pig and chicken liver being equally favorable. Apricots, peaches and prunes were greatly superior to the common vegetables, an observation which was explained by the presence of iron in combination with other important minerals. The remarkable response to liver was attributed not alone to the iron content but to the storage of organic factors concerned with hematopoiesis.

Recent studies have shown that the total iron content of foods does not correspond to its utilization for hemoglobin formation. With the aid of Hill's dipyridyl method, Elvehjem and his associates<sup>27</sup> have determined the inorganic iron fraction of various foods. The availability of this portion for hemoglobin regeneration as distinguished from the hematin or organic iron was demonstrated by appropriate feeding experiments with anemic rats. A direct quantitative relationship existed between the amount of iron determined by the reagent and the hemoglobin formation in these animals. The iron composition together with the available fraction of a small group of foods as determined by these investigators is listed in the following table:

TABLE 3  
AVAILABLE IRON AS COMPARED WITH TOTAL IRON  
(After Kohler, Elvehjem, and Hart<sup>27</sup>)

Foods.	Total Fe (per gram dry material).	Available Fe (per gram dry material).	Per cent available.
Lima beans.....	0.074	0.054	73
Lima beans.....	0.074	0.052	70
Peas (canned).....	0.122	0.110	90
Peas (fresh).....	0.118	0.085	72
Bananas.....	0.014	0.0086	61
Apricots.....	0.043	0.021	50
Lettuce (Batch 1).....	0.230	0.066	28
Lettuce (Batch 2).....	0.304	0.064	21
Parsley (dried).....	0.304	0.069	23
Spinach (fresh).....	0.352	0.067	19
Beef liver (Batch 1).....	0.260	0.180	69
Beef liver (Batch 3).....	0.181	0.130	72

The availability of iron for hemoglobin formation was also studied by Summerfeldt<sup>28</sup> from the standpoint of its solubility. This was estimated from the interaction of various foods with an artificial gastric juice similar in composition and in reaction with that of children between the ages of three and twelve years. The amount of iron brought into solution was found to compare favorably with the fraction utilized for hemoglobin formation as tested in anemic animals. Decreased

solubility values, however, would probably have been obtained on exposure of these foods to a medium similar to that of the gastric juice of infants. The value of foods for their iron content will probably be appraised in the future in relation to the component which is soluble and available for hemoglobin regeneration.

The necessity of copper as an adjuvant to iron in hemoglobin synthesis in experimental animals has been established but whether a deficiency in this element can occur with the ingestion of the ordinary diet has been debated. In the young infant on a sustained milk diet deficient copper stores are conceivable so that copper content of various foods assumes importance. Of 159 samples of common foods analyzed by Lindow, Elvehjem and Peterson<sup>29</sup> the copper content ranged from 44.1 mg. of copper per kilogram of fresh calf liver to 0.1 mg. of copper per kilogram of fresh celery. Within this range the following foods may be included as possessing a copper content above the average, and many of them with the proper preparation may be adapted for use during infancy: artichokes, lima beans, oatmeal, mushrooms, wheat bran and wheat germ, apricots, prunes (both dried), calf and beef liver, cod fish, lamb chops, chicken (dark meat) and egg yolk.

Liver may be regarded as the most important food offered to the infant for the prevention and treatment of nutritional anemia for it constitutes a rich source of iron and copper and of organic factors required for red blood cell and hemoglobin formation. The difficulties encountered in feeding adequate amounts of liver, even to older infants, necessitate resourcefulness in its preparation. After a short period of boiling or broiling, it may be scraped, minced or ground; while at times, feeding is facilitated by changing off from calves' liver to beef or chicken liver. The parenteral injection of various fractions of liver and treatment by various concentrates as substitutes for the whole organ are unnecessary, especially when it is realized that the guiding principle in the treatment of nutritional anemia is to overcome an iron deficiency. It should be emphasized that iron in adequate dosage constitutes the most effective weapon

in combating this form of anemia in infants and that it surpasses in potency and in rapidity of action any of the food-stuffs enumerated. The latter are essential, however, as sources of iron to meet the daily requirement and to provide stores for future needs, not alone of iron but of other factors that enter into hemoglobin synthesis.

A discussion of the management of nutritional anemia would be incomplete without mention of the rôle of vitamins and of heliotherapy. It can be said for the former that modern feeding takes cognizance of the need of an adequate supply of the most important vitamins from birth. Severe grades of rickets are at times observed without anemia; on the other hand, rickets may be cured leaving the associated anemia unaffected. Parsons and Smallwood<sup>30</sup> have pointed out that, excepting changes produced by hemorrhage in advanced cases of scurvy, there are certain hematologic features which serve to differentiate the anemia of infantile scurvy from those produced by iron deficiency. The ingestion of adequate amounts of the essential accessory food factors is not required for the cure of nutritional anemia, but it is nevertheless contributory toward the state of health essential for the maintenance of a normal hematopoietic balance.

As with the vitamins, it cannot be denied that sunlight exerts a beneficial effect upon the infant although the physiologic processes involved are not always obvious. The lack of exposure to the sunlight does not, however, precipitate nutritional anemia and the studies designed to determine the influences of irradiation upon the hemoglobin and red blood cells have led to contradictory results. In the evaluation of various antianemic agents, ultraviolet irradiation cannot be regarded as a dependable agent either for the amelioration or cure of nutritional anemia in infancy.

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### THE CARE AND FEEDING OF THE PREMATURE INFANT: WITH SPECIAL REFERENCE TO SIMPLE MILK MIX- TURES

THERE are three important considerations in the care of the premature infant, viz.: nursing, maintenance of body heat and feeding.

A good, careful nurse may mean the difference between life and death. She is worth a dozen incubators. The premature must be watched carefully at all times. Vigilance must never be relaxed, especially during the first two weeks of life. Every detail is important. Handling should be reduced to an absolute minimum. The infant should not be taken out to nurse or lifted from its crib to be fed. Daily weighings are unnecessary. This may be done every second, third, or fourth day, depending upon the condition of the baby. Oil baths can be given every other day. For the first forty-eight hours it may be best to leave the premature absolutely alone except for feeding and to treat symptoms only as they arise. After being oiled at birth the infant should be wrapped in a jacket of cotton wadding and placed in his crib in the Fowler position. The jacket is not absolutely necessary if an incubator is used. The Fowler position is preferred because it is the position favored in cerebral hemorrhage and cerebral hemorrhage is a common finding in these cases. Respiration also seems easier with the head elevated. In this position the infant can more readily be observed. His importance as a sick individual in a crowded nursery is emphasized. Occasionally, edema of the extremities

or scrotum may develop when the infant is kept so for too long a time. Placing him flat on his back will cause a disappearance of this swelling.

Twenty cc. of blood should be given intramuscularly if there is suspicion of cerebral bleeding. In fact, some observers go so far as to advocate the use of blood intramuscularly as a routine procedure in the treatment of all premature infants. Oxygen with from 5 to 10 per cent carbon dioxide or, preferably, oxygen alone is also of distinct advantage. It certainly is indicated when cyanosis is present. A concentration of 40 per cent oxygen is desirable. The oxygen tent is the method of choice but it is not always available. A funnel held close to the nose has given complete satisfaction. Nasal catheters have not proved satisfactory for they plug easily and, if kept for too long a time in the nasal orifices, will injure the delicate mucous membranes.

Maintaining body heat is the second important consideration. This is best accomplished by a mechanical incubator heated with electric bulbs. Such an apparatus is not difficult to construct. Electric bulb heating is preferable to the use of hot water bottles because the latter require frequent changing. The importance of humidity has also been emphasized by Blackfan and Yaglou. In order to determine the optimum environmental temperature and humidity for various groups of premature infants, different fixed percentages of relative humidity were maintained by them in nurseries by means of an air-conditioning system, and the dry bulb temperature was adjusted by trial to the level needed to stabilize the body temperature. At first, relative humidities of 20 and 80 per cent were tried, but later they were changed to 30 and 65 per cent, as it was found that relative humidities above 65 per cent were distressing to the attendants and symptoms of dehydration frequently occurred in premature infants when the humidity was kept below 30 per cent over a considerable period. With a relative humidity of 65 per cent the air temperature required to maintain equilibrium of body heat in infants weighing from 3 to 5 pounds was found to be about 77° F. When the relative

humidity was reduced to 30 per cent, however, it was necessary to increase the temperature to 80° F. Alternate exposures to each of these two air conditions for a week at a time resulted in no significant difference in the stabilization of body temperature. But in prolonged exposures to relatively low humidity, marked differences developed. If kept up for two weeks or longer, it tended to promote instability of body temperature, and general disturbances, such as diarrhea, fever and vomiting, were increased. Gains in weight were generally reduced and fatalities increased. Continuous exposure to high humidity, on the other hand, gave satisfactory results. The effects of intermediate humidities were also studied, but a relative humidity of 65 per cent was found to be more advantageous than any of the other values tried.

With this humidity the temperature requirements ranged from 75° to 100° F., depending on the general condition of the infant and the body weight. Infants under 3 pounds at times required the higher temperatures, 90° to 100° F., to maintain a normal rectal temperature, but this need was often only temporary.

Maintaining a relative humidity of 65 per cent is difficult in nurseries heated by radiators and ventilated by normal means, particularly in cold weather. A large quantity of water must be evaporated to reach this point of humidity and this can be accomplished satisfactorily only by the use of mechanical humidifiers, since the actual moisture content of cold outdoor air is very low compared with what is required indoors. For example, if a room 12 x 15 x 10 feet is to be kept at 77° F. and at a relative humidity of 65 per cent when the outdoor temperature is 20° F. and the outdoor relative humidity 65 per cent it would be necessary to evaporate a minimum of 3 pounds of water per hour in order to maintain the desired humidity. This is with natural ventilation through windows and doors to the extent of about two changes of air per hour. With 25 changes of air per hour, as in Blackfan's investigation, 37½ pounds or 4½ gallons of water must be evaporated per hour to produce the optimum results. From these figures it is

easy to see that evaporation from a pan of water on the radiator, or from a wet sheet, would be entirely inadequate.

A subnormal temperature, particularly in the low weight groups, is a characteristic of prematurity which Blackfan believes should be preserved. Attempts to force the body temperature of these small infants to the supposedly normal level of  $98.6^{\circ}$  F. should be discouraged as in a number of instances such a practice was followed by overheating with its resultant serious consequences. This view is by no means unanimous as many observers feel that the infant's temperature should be maintained above  $98^{\circ}$  F. and below  $100^{\circ}$  F. Naturally, if the temperature rises above this, steps are taken to lower it. Temperatures from  $100^{\circ}$  to  $102^{\circ}$  F. for periods as long as twelve hours and more have often been seen in premature infants, however, without deleterious effects. These infants should never be permitted to become chilled as serious consequences may supervene.

#### FEEDING

In the feeding of the premature, breast milk has been looked upon as the "sine qua non." The doctrine has often been promulgated that it is the only safe food for such infants and that any success with artificial mixtures is solely a matter of luck. Such a belief is a relic of the days when unhygienic methods in the collection, transportation and storage of cows' milk often made it unsafe for human consumption, especially those born before term. These conditions still exist in certain communities, but when one can be assured of clean cows' milk, its use in the feeding of premature infants is safe and, for many reasons, often desirable.

There can be no quarrel with the stand that breast milk is the most desirable food for the normal newborn infant. With the premature certain other factors must be considered. Breast milk is at times difficult to obtain as the child's own mother generally leaves the hospital after two weeks and milk from other patients may not be available. If the mother has to pump her own breasts and deliver the milk, it may be difficult for economic or physical reasons for her to do so. Mothers'

milk may be purchased but it is expensive and such an expense is often a burden to the family. In addition, breast milk containing but 1.5 per cent protein hardly seems suitable for the needs of such a rapidly growing organism as the premature infant. Therefore, in spite of the fact that an imposing array of statistics has been advanced to prove that breast-fed infants are less likely to suffer from respiratory and gastro-intestinal disorders than those artificially fed, it is felt that the sacrifices usually made to obtain breast milk are hardly necessary, especially since adequate substitutes are readily available. Among these substitutes may be mentioned evaporated milk, lactic acid or protein milk mixtures. The feeling has existed that cows' milk could not satisfactorily be used as one of these substitutes but, in our hands, simple mixtures of cows' milk, water, carbohydrate in the form of dextri-maltose, and added protein in the form of calcium caseinate have given complete satisfaction.

During the first week of the premature's existence the important problem is to maintain life, not to produce a gain in weight. One must not try to force fluid intake. Our routine is to start feeding from six to twelve hours after delivery and to give a simple milk mixture, as will be outlined below, every three hours regardless of the weight of the infant and also a 5 per cent sugar solution every three hours. In other words, the infant receives some fluid every one and one-half hours. As the amount of formula taken is increased, the water feedings are decreased. It has been claimed that a premature requires in twenty-four hours about one sixth of its body weight in fluid inclusive of that in milk. However, this amount is not usually taken until well into the second week, sometimes not even until the end of the first month. The appetite of the premature is capricious. The amount taken at each feeding varies, especially during the first fortnight. In the smaller, weaker infants the intake is measured in drachms. One should not attempt to force feeding. One is not dealing with a balloon that has to be blown up. Food is cautiously and slowly increased as the infant evidences a desire to take more. The closer the infant is to term the more he may be expected to take, all other things

being equal. The use of hypodermoclyses to augment the fluid intake is unnecessary except in the exceptional case.

If the infant can suck on a nipple, he is fed in that manner. Otherwise, recourse must be had to a medicine dropper. A soft rubber tubing about three inches long and an eighth of an inch in diameter is attached to the lower end of a long dropper or eye pipet. The soft rubber tubing is inserted at the side of the infant's mouth and passed back to the base of the tongue, about 2 inches from the gum line. After the tip of the tube has reached the posterior wall of the throat, the bulb is gently pressed.

Occasionally, it may be necessary to feed by gavage. This is especially true when feeding produces cyanosis and it is desired to administer food with the minimum of discomfort. For gavage, a No. 12 French catheter may be used. This is marked at three different places: (1) the distance from the tip of the ensiform to the bridge of the nose; (2) 2 cm. above that; (3) 2 cm. above this last mark. When the catheter is passed to the first mark, the tip is from 1 to 2 cm. above the cardia. Feeding may be given then without entering the stomach. The catheter is always passed with the funnel empty. The barrel of an ordinary glass syringe makes a satisfactory funnel. If there is marked distention of the stomach, the catheter is passed to the second mark. Sometimes it is necessary to pass it to the third mark to empty the stomach of air. The average feeding time should be about three minutes. One must be careful to compress the catheter while it is being withdrawn.

Gavage feeding in expert hands may be without danger. One must not forget that it is always possible to enter the larynx and fluid may be accidentally introduced into the lungs. Some observers claim that this happens often enough to warrant the prohibition of this method of feeding. Although it has its advantages, especially in trained hands, we feel that it is not necessary as a routine procedure.

A series of sixteen premature infants under 4 pounds, all of whom had been under our care as private patients, were

CHART I

Name.	Sex.	Period of gestation.	Cause of prematurity.	Type of delivery.	B. wt.	Low point.				Weight.				Gain from low point.		Average gain per day.	Weight.		Type of feeding, remarks.
						Wt.	Age.	B. wt. reg. age.	1 mo.	2 mos.	Discharged.	Wt.	Age.	Ozs.	Days.		0 mos.	1 yr.	
I. S.	F.	28 wks.	Twins.	Vertex spont. Brother died breech.	2 <sup>10</sup>	2 <sup>1</sup>	7 days	24 days	2 <sup>16</sup>	4 <sup>1</sup>	4 <sup>15</sup>	4 <sup>15</sup>	10 wks.	43	07	0.65	Died of pneumonia age 3 mos.		Breast milk plus 7 to 10 per cent carbohydrate 1 month, then formula.
K.	M.	28 wks.	Toxemia.	Vertex spont.	3	3	1 day	1 day	4 <sup>2</sup>	7 <sup>1</sup>	5 <sup>1</sup>	0 wks.		33	41	0.8	12 <sup>12</sup>	17 <sup>1</sup>	Breast milk plus 7 to 10 per cent carbohydrate.
J.	F.	7 mos.	Toxemia.	Vertex spont.	3	2 <sup>12</sup>	0 days	12 days	4	8 <sup>4</sup>	5 <sup>4</sup>	0 <sup>1</sup> / <sub>2</sub> wks.		30	42	0.93	11 <sup>18</sup>	Left city	Breast milk plus 7 to 10 per cent carbohydrate and form. 3 weeks, then form.
B.	F.	7 mos.	Toxemia.	Vertex spont.	3 <sup>2</sup>	3	2 days	4 days	4 <sup>12</sup>	8	5 <sup>2</sup>	36 days		34	34	1.00	13 <sup>9</sup>	18	Breast milk plus 7 to 10 per cent carbohydrate and form. 3 weeks, then form. Alone.
T.	M.	28 wks.	Prev. left oophorectomy. Irreg. bleeding throughout preg. with partial prem. sep. placenta at onset of labor.	Vertex spont.	3 <sup>2</sup>	3	7 days	15 days	4 <sup>4</sup>	6 <sup>7</sup>	4 <sup>8</sup>	30 days		25	30	0.83	14 <sup>10</sup>	22	Breast milk plus 7 to 10 per cent carbohydrate and simple milk mixtures, 7 weeks then completely weaned.
Wago					3 <sup>1</sup>	2 <sup>12</sup>	5 days	11 days	....	....	....	....	....	....	43	0.82			



recently reviewed to determine the efficacy of simple milk mixtures in the feeding of such infants. Prematures over 4 pounds were deliberately excluded because feeding is usually much less of a problem in the heavier babies and the inclusion of these in a statistical study tends to increase the percentage of favorable results. Five of the 16 failed to survive. Three died within the first twenty-four hours and two expired at the age of six and seven days, respectively. Autopsy failed to reveal findings of significance except prematurity and, in addition, in one infant a subarachnoid hemorrhage was found at the base of the skull. Breast milk was given to all of these. The birth weight varied from 3 pounds to 3 pounds 10 ounces with an average of 3 pounds 4 ounces.

Five infants received breast milk reinforced with 7 to 10 per cent carbohydrate. Simple milk mixtures were gradually substituted after a period varying from three to seven weeks. Chart I illustrates the findings in this series.

The third group consisted of six infants who received milk mixtures commencing six to twelve hours after birth. Chart II best illustrates our results with these infants. Attention is called to the high caloric intake and the high concentration of carbohydrate employed. Sugar was formerly considered a major factor in the production of diarrhea in the infant, but such a premise is no longer tenable and we have found concentrations of carbohydrate from 10 to 17 per cent most helpful in producing weight increases.

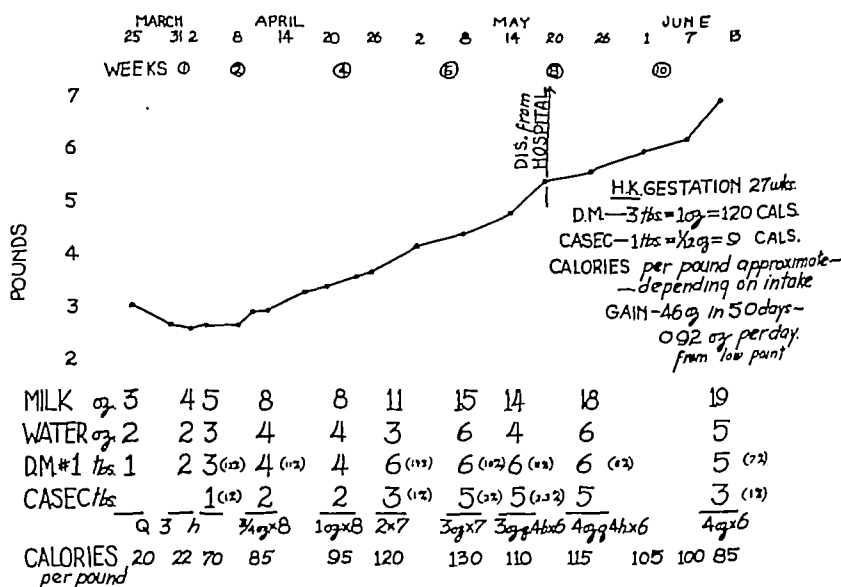
Chart III illustrates the type formula used and the rate of increase carried out in feeding these infants. The addition of 1 to 3 per cent protein in the form of calcium caseinate (casec) was thought helpful in stimulating weight increases. The three-hour interval was maintained until a weight of  $4\frac{1}{2}$  pounds was reached, when the night interval was increased to a four-hour one. At 5 pounds the four-hour interval was adopted for the entire twenty-four hours and at about  $5\frac{1}{2}$  pounds the 2 A. M. night feeding was omitted so that but 5 feedings (q 4 h) were given in the twenty-four hours. Vitamin D in the form of 10 drops of viosterol was given as soon as it was felt that the child

CHART II

Name.	Sex.	Period of gestation.	Cause of prematurity.	Type of delivery.	B. wt.	Low point.		Weight.					Gain from low point.		Average gain per day.	Weight.		Type of feedings, remarks.
						Wt.	Age.	B. wt. reg. age.	1 mo.	2 mos.	Discharged.		Ozs.	Days.		6 mos.	1 yr.	
											Wt.	Age.						
P. H.	M.	7 mos.	Twins (other died following version and extraction). Wt., 3 lbs.	L. O. A. spont.	2 <sup>s</sup>	2 <sup>1</sup>	7 days	13 days	3 <sup>s</sup>	4 <sup>s</sup>	0 <sup>13</sup>	4 mos. 1 wk.	73	117	0.02	10 <sup>1</sup>	15 <sup>11</sup>	Milk mixture. Calcium caseinate added, ago 12 weeks.
J. N.	F.	27 wks.	Calcium def.	Vertex spont.	2 <sup>11</sup>	2 <sup>s</sup>	6 days	20 days	3 <sup>s</sup>	5	0 <sup>1</sup>	11 wks.	60	70	0.80	12 <sup>s</sup>	....	Milk mixture plus calcium caseinate.
H. K.	M.	27 wks.	?	Vertex spont.	3	2 <sup>s</sup>	5 days	19 days	4 <sup>s</sup>	5 <sup>s</sup>	5 <sup>s</sup>	8 wks.	46	50	0.02	14	21	Milk mixture plus calcium caseinate.
N.	F.	7 mos.	?	Low for- ceps L. O. A.	3 <sup>s</sup>	3 <sup>s</sup>	3 days	5 days	5 <sup>s</sup>	7 <sup>1</sup>	5 <sup>s</sup>	1 mo.	33	28	1.14	14 <sup>10</sup>	20	Milk mixture.
W. U.	M.	8 mos.	Toxemia.	Vertex spont.	3 <sup>s</sup>	3 <sup>s</sup>	2 days	4 days	0	8 <sup>10</sup>	5 <sup>14</sup>	4 wks.	38	20	1.40	14 <sup>s</sup>	19	Milk mixture plus calcium caseinate.
A. B.	F.	8 mos.	Contracted pelvis, Prem. rup. memb.	Ces.	3 <sup>14</sup>	3 <sup>10</sup>	2 days	4 days	5 <sup>s</sup>	7	5 <sup>s</sup>	1 mo.	30	29	1.00	13 <sup>s</sup>	21 <sup>s</sup>	Milk mixture.
Average	.....	.....	.....	.....	3 <sup>s</sup>	2 <sup>14</sup>	4 days	11 days	....	...	....	....	....	53		1 oz.		

stood a chance of surviving. Orange juice was started at the end of the second month. Egg yolk, cereal and vegetables were added in that order some time between the fourth and sixth months, depending on the child's progress. As soon as possible the 10 o'clock night feeding was discontinued and but 4 feedings given in the twenty-four-hour period. A 3-feed-

CHART III



ing schedule was instituted at the earliest opportunity, usually between the seventh and eighth months, at which time meat was added.

In the feeding of these infants, as well as in the feeding of the normal infant, every attempt should be made to simplify the procedure so that the mother's burden is made as light as possible.

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### THE MANAGEMENT OF RHEUMATIC HEART DISEASE

WHENEVER one becomes interested in a certain disease, it is a great temptation to become so absorbed in it that each observation, new to oneself, seems startling and important. It is a salutary and humbling thing to go back in medical history and learn how long ago physicians equipped only with their senses and with no instruments of precision noted clinical conditions which we are rather wont to consider something new under the sun. Storck, for instance, described rheumatic pleurisy in 1762, and in 1776 Van Swieten recognized that the heart becomes involved in rheumatism. He said, "Sometimes when the pain of rheumatism in the limbs ceases there arises an anxiety of the breast, a palpitation of the heart and an intermitting pulse." David Pitcairn lecturing at St. Bartholomew's Hospital about 1788 taught that acute rheumatism and heart disease were but different manifestations of the same disease. But although study of the heart received great impetus from the invention of the stethoscope by Laënnec in 1819 this conception of heart disease as being an integral part of the picture of rheumatic infection did not receive wide acceptance for many years.

In 1843 Sir Thomas Watson pointed out that children as young as three or four years might develop carditis and said that the earlier they had acute rheumatism the more certainly was the heart involved. Two years later Latham said, "Listen every day to the cases of rheumatic fever, for the endocardial lining may be involved even in the mildest cases." And these

are points which those of us who have studied rheumatic heart disease particularly in children are apt to stress as if it were something of a new idea.

Yet, as far as the human race goes, two hundred and fifty years or so is a short time, and it is during such a period that our knowledge of the clinical aspect of rheumatic fever has become defined, and the sociological importance of the disease has become clear.

In focussing our attention on rheumatic fever, in showing us how to study it, in delineating its complicated features, and in making fundamental studies, there is no one to whom modern medicine owes a greater debt than to Homer Swift.

The title given me to speak on, the management of rheumatic heart disease, is so comprehensive that it will be impossible to cover every important aspect. I shall therefore discuss first the general aspects, and then a few special procedures which we have found useful on the Children's Medical Service at Bellevue Hospital.

I have already said how much was known long ago about the clinical aspects of the disease, and even how some physicians had a conception of it which approximated the present one. The most important advance in recent years is, I think, the realization that the consideration of any aspect of rheumatic heart disease cannot be divorced from a consideration of rheumatic fever as a whole.

It is unfortunate that the care of adults and children should be separated as it is. Certain conditions in infancy and childhood demand special training and experience, and only those who care about children, just because they are children, will become equipped to handle these matters. But when a disease which is not wholly confined to one age group is studied during *one phase by pediatricians and during another by physicians* who handle adults, considerable gaps in the care of the patients are bound to occur. For instance, one of the most important features in the management of rheumatic heart disease is that of the care of ambulatory patients. At Bellevue Hospital there is an adult cardiac clinic run by physicians connected with New

York University. This clinic has a large group of rheumatics and accepts patients over the age of twelve. Our children's cardiac clinic, with the same medical school connections carries a large group of children (between 600 and 700) through the age of sixteen. Some of our children when they reach this age are willing to go to an adult clinic. But many of them become independent, and often resentful of too much supervision. If they feel well they dislike to admit that they have any physical handicap. Consequently in spite of friendly cooperation between the clinics a considerable number of them are lost as to adequate medical supervision during the period of adolescence, a period which must be just as important to them in terms of keeping fit than either early childhood or adult life. Instead of having cardiac clinics it would be more logical to have rheumatic clinics, for the care, as a group, of patients of all ages who have had any form of rheumatic fever. This would lead to better continuity in the observation of patients, and should avoid the loss to medical care of individuals of the adolescent group.

The purpose of a clinic should be two-fold; first the care of the patients, and second the accurate recording of data so that information can be acquired which will lead to better knowledge of the disease and hence better care of the patients. In the relatively short time during which I have been interested in rheumatic fever I have been aware of a change in the general attitude toward rheumatic heart disease. This in New York City has been largely due to the work of the New York Heart Association which has stimulated cardiac clinics to organize on a basis which would contribute to the knowledge of heart disease, without interfering, in any way, with the care of the patients. As a matter of fact, clinics run on such a basis are far more apt to give patients intelligent, conscientious supervision than those less well organized. The extent of the work that the research service does is indicated by the fact that there have been collected 20,000 records of cardiac patients, most of them from 24 clinics in New York City which cooperate with this research service. Analysis of these records is capable of

showing the course of the various heart diseases, and the influence of organized systematic care.

In managing ambulatory patients with rheumatic heart disease two questions must always be uppermost. First, and most important; is the infection active? Second, does the patient show any evidence of heart failure?

The first question, is the infection active, is the most difficult to answer. A frank attack of polyarthritis, or pericarditis, with fever and other evidence of acute infection is simple enough to identify. But we know that many patients who have never had symptoms are found on entering school or when applying for working papers to have definite evidence of heart disease. About 20 per cent of children with heart disease of the rheumatic type in the Bellevue clinic have never been ill with any form of recognized rheumatic infection, and until the chance discovery of heart disease were unaware of the existence of the handicap. This lends emphasis to the belief that a large part of rheumatic infection of the heart is subclinical. In other words, before the inflammatory process in the heart has gone far enough to produce physical signs or definite symptoms of damage, fairly extensive involvement may already have occurred. This fact is reason enough for careful supervision and frequent observation of patients who have ever had any manifestation of rheumatic infection. One should assume, in spite of the absence of proof, that the heart is always involved, even when the manifestation is only chorea. A case occurred on our service at Bellevue a few years ago which brought this point home. A girl of twelve died accidentally toward the end of an attack of chorea. She had had two previous severe attacks, one of them in Bellevue, and had been observed regularly in the clinic. During none of her attacks did she show any of the evidence of what we consider proof of the presence of active infection. She had at no time had fever, tachycardia, elevation of the white blood cells or polynuclears, or enlargement of the heart. She had had an inconstant systolic murmur heard just to the left of the sternum, the type commonly interpreted as being functional or accidental. At autopsy, however, there was endo-

carditis of the mitral valve, and evidence of past inflammation of the aortic valve. Another case was striking in another way. A two-year-old boy had been on the ward with paratyphoid infection—the first illness he had ever had. At that time it was noted that he had an enlarged heart and a loud harsh systolic murmur widely heard but maximum in the third and fourth spaces close to the sternum. A tentative diagnosis of congenital defect of the heart was made. Two days after discharge he was readmitted with high fever and swelling of the back of one hand. Examination of the heart showed no change. His temperature came down and the swelling disappeared, leaving him with the aspect of a poorly nourished, chronically ill child. One day his father brought him a balloon and he played with it rather actively in bed. Soon after he suddenly dropped dead. Autopsy showed extensive endocarditis and myocarditis, definitely rheumatic in type. These two cases are extremes, but show clearly how inadequate are our clinical resources in proving the presence of active inflammatory processes in the heart. Even the erythrocyte sedimentation rate is not an infallible guide; we have had a number of children with active carditis, even pericarditis, who had consistently normal sedimentation rates.

The first step, then, in the intelligent management of rheumatic cardiacs is to realize that active infection may be present without clear-cut evidence. It is the repeated doses of infection, either the subclinical or the acute, which cause eventual deformity of the heart and permanent interference with its functional ability. Once this conception is clearly in mind the importance of identifying rheumatic individuals and of giving them meticulous care during the very beginnings of their disease becomes obvious. What this care should consist of can be stated in very general terms. Since rheumatic fever is an infection the exact etiology of which is still unknown, the best we can do is try to help each individual to keep as close to his optimum state of health as possible in order to increase his resistance to infection. This means attention to his diet, his daily régime, the amount of rest and of recreation he gets. If



he already has heart disease, his activities should be regulated so as nearly to approximate his full capacity, but never quite reach it or to go beyond it. It may mean removing infected tonsils and the care of any other abnormal condition. It means keeping an alert eye for the slightest suspicion of reappearance of the rheumatic infection.

The management of a clinic patient who is suspected of having subacute rheumatic infection is always difficult. He is not sick enough to be hospitalized, and if told to go to bed at home is quite likely to be unwilling to do this. I wish that instead of having cardiac convalescent homes we had institutions designed to take the very early, the subclinical, type for prolonged care such as patients in the early stages of tuberculosis can get. This will probably eventually happen, but not until we get away from the emphasis on heart disease, and think wholly in terms of the rheumatic infection, of which heart disease is the most serious and disabling end-result. Prolonged bed rest under good hygienic surroundings is a primary requirement for the treatment of rheumatic heart disease in its very early as well as late stages.

Little more can be said actually about the management of ambulatory patients. With the exception of digitalis, no drug is of particular importance, as far as the heart itself goes. Secondary anemia which is fairly common in these patients should be treated appropriately. The indiscriminate use of salicylates or similar drugs is to be deplored, since they may mask symptoms which would be important in recognizing activity of the infection. In fact, I think these drugs should never be given over a period of time except when the patient is in bed and under close observation. This is not to say that these drugs are not of great value in the treatment of certain phases of rheumatic fever, but the idea that they should be given over periods of months to ambulatory patients with the idea of preventing recurrences seems to me to be very questionable.

Digitalis is of considerable value in the treatment of ambulatory cardiac patients, even in the absence of auricular

fibrillation, where its value is unquestioned. Several children in our clinic take digitalis regularly. One is a particularly interesting case. She first came to Bellevue at the age of 6 in 1932 in heart failure evidence by cyanosis, tachycardia and great dyspnea. The massive dose method of digitalization caused the signs of failure to disappear, and the heart rate came down to normal. The maintenance dose was discontinued after she had been up and around for a time and she was discharged. She returned in a few weeks again in failure, and the story was repeated a second and then a third time. She is now on digitalis regularly, and as long as she takes 1 cat unit a day she is comfortable, active, attends school and is functionally in class 11A. This is an unusual case, but there are others who with digitalis lead a relatively comfortable life. When the drug is omitted, the heart rate gradually creeps up again and symptoms of failure begin to recur, usually in two to three weeks. These children are given an amount of digitalis necessary for one or two weeks, and return regularly for examination and further supply. They are carefully instructed in the symptoms of overdigitalization and no difficulty has been encountered with this. The need for digitalis only occurs in the rather badly damaged heart, so that it can be thought of almost as a life-prolonging last resort.

Rheumatic patients should be taught to have great respect for colds and sore throats. It happens over and over again that a pharyngitis or tonsillitis in a rheumatic subject is followed in ten days or so by a flare-up of the rheumatic infection. It is quite true that this sequence of events does not always follow but it happens so frequently that one cannot escape the conclusion from purely clinical observation that there is a relationship of some sort. Patients should not only take care of themselves during even a mild cold by going to bed for several days, and perhaps using local treatment, but should avoid possible contacts with individuals who have colds. Following a cold they should be examined carefully for several weeks for evidence of infection. Whether this type of care accomplishes

anything I am not certain, but it is a relatively simple precaution to take.

The management of in-patients with rheumatic heart disease is quite a different matter. They are usually acutely ill, at least when they are first admitted to the hospital, and the relief of symptoms is the first concern. First and foremost, as always, the patients need rest as complete as possible whether they have acute carditis with or without failure. Sedatives or narcotics should be given in sufficient quantity to make the patient quiet and as comfortable as possible. If after a few days the signs of failure have not diminished on rest alone, digitalis should be given. If optimum dosage of this drug is insufficient to control the failure altogether, theocin may be administered. If this is unsuccessful in getting rid of accumulated fluid, a mercurial diuretic may be used. In general, however, if rest and digitalis is not enough, one can assume that there is an extreme grade of myocardial involvement, and that even though the failure is relieved by other means, the prognosis is grave. Congestive failure in itself is a serious manifestation, and there is a limit to the number of attacks which a patient can survive. The greatest number of attacks of congestive failure I have seen occur in one child was eight. This boy was extraordinary from several points of view. He was under close continuous observation from the age of five until his death at eleven, and he had had auricular fibrillation since the age of six and one-half. Each attack of failure occurred following a fresh exacerbation of rheumatic infection, several times while he was taking a maintenance dose of digitalis. He finally died in congestive failure. Only the care which this boy received and the constant use of digitalis kept him alive so long.

Failure is almost certain to follow pericarditis, which is probably the most severe manifestation which rheumatic carditis can take. We now at Bellevue give digitalis at the beginning of an attack of pericarditis with the idea that since signs of failure are practically sure to follow, the failure may be more easily controlled if the drug is given early. This procedure has only been followed for the past year or so, and

whether it is of value in checking the development of the signs of congestive failure cannot be determined until a careful analysis of the records has been made and compared with those of patients not so treated.

The incidence of pericarditis varies from year to year, just as the severity of rheumatic fever varies. Last year, for instance, was a relatively light year at Bellevue, at least among the children, and for the first time in years there were several periods when there were no patients who showed rheumatic nodules. This year on the other hand, the rheumatic season began early with unusually severe attacks of the disease.

For the treatment of the pericarditis, which implies the presence of a pancarditis, absolute rest is essential, with drugs if necessary to secure this. Pain, which is often referred to the left shoulder, is by no means the rule, but when present is controlled better by drugs than by ice-bags or hot water bags over the precordium, although sometimes patients are relieved by these measures.

With rare exceptions, the course of an attack of pericarditis is a stormy one. The patient is acutely ill, and looks like a very sick pneumonia. Sometimes the toxicity of the process is so great that the patient succumbs within a few days, but more often it goes on to the development of pericardial fluid.

This significance of the posterior chest signs developing during pericarditis was brought to our attention by Connor's paper "On the Diagnosis of Pericardial Effusion." He pointed out that these signs indicate the development of a moderate or large amount of fluid in the pericardial sac. Probably some fluid always develops following fibrinous pericarditis, although not always in sufficient quantity to allow an absolute clinical diagnosis. If the fluid develops slowly distressing symptoms may not follow, but more often the patient is made distinctly uncomfortable. Williamson and his coworkers pointed out that sudden death may be due to too great intrapericardial pressure caused by large amounts of fluid and felt that even in rheumatic subjects relief of this pressure by removal of the fluid might be justified. His articles led us to study the matter.

Cohnheim, many years ago had demonstrated that injection of fluid into the pericardial sacs of dogs raised the blood pressure. He was able to cause cessation of the heart beat in these animals by increasing the intrapericardial pressure in this way. When the pressure was decreased by out-flow of the fluid from the sac, the heart resumed beating even though it had been quiescent for two to three minutes. At the same time the blood pressure came back to normal. Because of this work, the investigations of Williamson and others, and our own observation, we feel that the blood pressure can be used as a guide to indicate the necessity for tapping the pericardium. When clinical evidence of fluid begins to appear, the blood pressure should be taken daily, or oftener. If it is rising, if the patient is becoming more cyanotic, weaker, more dyspneic, coughing more, and complaining of a sense of suffocation, and if posterior chest signs have developed we feel that the pericardium should be tapped. Going in posteriorly is as simple and safe a procedure, providing the amount of fluid is large enough to have produced these signs, as a pleural tap. The improvement in the patient's condition, and the relief of distressing symptoms following decrease in the intrapericardial pressure is sometimes very dramatic. After the tap the intensity and extent of the posterior signs may be very much diminished. Although we are not convinced that this procedure makes much difference in the progress of the disease, it has in several instances seemed to be a life-saving procedure, and in all cases, the patients have symptomatically been improved.

Following an attack of acute carditis, the patient, if he survives, goes into the prolonged subacute phase of the infection, which may last for months or years. The evidence indicating the persistence of the active process may be slight, for instance only tachycardia present during sleep as well as during the day, and occasional slight rises in temperature. Or there may be erythema marginatum, or gallop, or loss of weight. Meanwhile, the inflammatory process in the heart is going on, or if gradually subsiding, the healing process of fibrosis is progressing to produce more deformity of the heart structure.

So far, effective therapy at this stage is confined to bed rest plus nursing care, adequate diet and dealing with such factors as the secondary anemia and foci of infection.

It is possible, however, that fever therapy, which in general is indicated in subacute infections which are not virulent enough to stimulate the body's own defense mechanism, may be of value in certain cases. While the value of fever in the treatment of chorea was being investigated at Bellevue Hospital, it was noted that several of the children who had definite evidence of carditis of not severe grade at the same time lost these signs soon after the fever therapy which was given for the chorea. After the observation was first made such patients were watched closely. It was found in the series of 150 children with chorea treated by means of fever that 16 had active carditis. Of these, 9 had lost the signs of activity by the time the treatment for the chorea was finished, and the remainder were clinically inactive within seven to ten days later. As a result of our own observations, we were led to treat with fever therapy a small number of children in the subacute phase of rheumatic carditis. Radiant energy, rather than a foreign protein was used to produce fever. The cases were carefully selected from two points of view. First, since the procedure seemed a rather radical departure, patients who appeared to be in sufficiently good general condition to stand a fever of between  $105^{\circ}$  and  $106^{\circ}$  F. for five hours were chosen. Second, only patients with clear-cut evidence of active carditis were treated, since in order to evaluate the results findings which could be said definitely to be present or absent had to be used. Groups of signs such as persistent tachycardia, loss of weight, gallop, fever, nodules, or rash were the criteria used. The few patients who have been so treated have done well. By that I mean that soon after the treatment the signs of activity have either disappeared or noticeably diminished. From only a few cases no conclusions can be drawn, other than that such patients stand fever therapy well, even when there is extensive damage to the heart.

The only reason for mentioning, in a paper of this sort, a

procedure which is entirely experimental is to reemphasize the point that if far-reaching results are to be accomplished therapeutically with rheumatic heart disease, treatment must be directed both toward preventing the development of active infection, and toward inhibiting the process once it has started. Treatment of already established heart disease is almost entirely symptomatic and palliative. While we must, of course, do our best to care for these patients, we should keep constantly in mind the wider viewpoint, the importance of which I have tried to demonstrate.

The death rates from rheumatic heart disease show that it is still a formidable enemy of childhood and adult life, even though the death rates from acute rheumatic fever have steadily declined over a period of years. This probably means that the percentage of the population which is partially incapacitated by this form of heart disease is greater than before. There is, however, some evidence to indicate that organized care, and the increasing interest in rheumatic fever may have had some influence on the death rate in the lower age group. Eventually the proper management of these patients can be defined in much more certain terms than I have been able to do here; but not, I am sure, until the emphasis is consistently put not on rheumatic heart disease, but on the recognition of the presence of the rheumatic infection in its earliest phases; nor until organized care is devoted largely to those rheumatic patients who have not yet developed advanced heart disease.

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SOME CLINICAL ASPECTS OF PERIARTERITIS NODOSA

THE tendency to regard periarteritis nodosa as a rare pathological lesion of academic interest is rapidly losing ground. While contributions on its pathogenetic relationship to common disorders (hyperergy, malignant nephrosclerosis, arteriosclerosis, purpuric and erythematous skin lesions) still dominate the literature, increasing attention to its variegated clinical picture and more frequent consideration in differential diagnosis has led to widespread recognition of its practical importance and a rapidly mounting number of correct antemortem diagnoses has resulted. As this report is intended to stress clinical aspects, many equally interesting phases have been omitted; moreover, since practically any of the smaller muscular arteries (or groups of arteries) may be affected and since almost every new case presents some unusual features, it has seemed advisable to restrict discussion to the symptoms more frequently encountered. An abbreviated case report follows:

C. S., white male, aged twenty-six, admitted October 26, 1935, died December 9, 1935.

On October 17, 1935, he experienced some pain in the calves which he attributed to bowling. On October 19th, both ankles were swollen and slightly tender. The leg pain increased until he was unable to walk on October 22nd. He had not previously eaten pork and did not work with any heavy metal. His previous history was negative except for pneumonia at eight, tonsillectomy at eleven and an upper respiratory tract infection, one week prior to his present illness.

On admission the physical examination was negative with the following exceptions: slight postnasal discharge and x-ray evidence of frontal and maxil-



lary sinusitis; systolic apical murmur; few discrete shotlike inguinal glands; intense pain on pressure of calves and in popliteal space; moderate swelling of the left wrist.

On November 1st, pain in the lumbar region and insomnia appeared. Routine chest plates revealed an infiltration in the right upper lobe, but there were no confirming physical signs and repeated sputum analyses and gastric lavage for tubercle bacilli were negative. The late afternoon and early evening temperature persisted, varying from 99° to 102° F., with extremes of 98° and 102.8° F. The pulse closely followed the temperature and ranged from 74-120. The minimum blood pressure was 100/60, the maximum 120/74.

On November 12th, there was impaired percussion in the right upper lobe. occasional fine râles; x-ray plates, similar to those previously taken. The Department of Tuberculosis reported that "the clinical picture, physical findings and x-ray films are not consistent with a diagnosis of tuberculosis."

By December 1st, the complaints had disappeared and the patient was mildly euphoric. However, he had lost considerable ground; marked loss of weight, increased cachexia, sallow face; café au lait appearance.

On December 6th, he suddenly became dyspneic and there was an expiratory grunt. Respirations which had been 22 suddenly rose to 44-50. Pulse 104; temperature 100.2° F. The blood pressure rose to 178/110. Râles in the chest became larger and the breath sounds exaggerated. The pulse rate increased (120) and the respirations were shallow and rapid. Death on December 9th.

The following is abstracted from many laboratory examinations:

Muscle biopsy revealed neither parasites nor vascular changes. Inguinal lymph gland biopsy showed "non-specific endothelial hyperplasia." All of many urine analyses showed albumin in increasing amounts; at first occasional hyaline casts, later many hyaline and granular casts; red blood cells in only one specimen. Early blood chemistries were normal; no report on terminal status. Blood Wassermann and gonorrhea complement fixation negative. Many blood cultures negative. Agglutination for typhoid, paratyphoid, and melitensis negative. Red blood cell count showed a gradually increasing hypochromic anemia going from 4,900,000 on admission to 3,332,000 at death. White blood cells on admission 22,000; weekly blood counts showed no change except an unexplained rise to 40,850 the second week of hospitalization and a terminal decline to 16,100. Eosinophiles usually 1 per cent; 3 per cent in one count. Platelets averaged 225,000. One specimen of feces showed ova of *Ascaris lumbricoides*; no other parasites found in several examinations. The sedimentation time gradually increased from 20 to 65 (one-hour readings) during hospitalization. Icterus index 17; van den Bergh—positive delayed. Electrocardiograms negative.

The presumptive clinical diagnosis was: periarteritis nodosa. Terminal bronchopneumonia. The postmortem diagnosis follows (Dr. A. Saccone):

*Gross anatomical diagnosis:* periarteritis nodosa of internal organs; acute nephritis; peritonitis; hypertrophy of heart with myocardosis; hepatosis; hyperplastic splenitis; chronic vegetative endocarditis; passive congestion of liver with terminal sepsis(?). The *microscopic diagnosis:* renal periarteritis nodosa; periarteritis nodosa of periadrenal tissue and of coronary vessels; old periarterial lesions of liver and pancreas (hepatitis and pancreatitis); passive congestion of liver; hyperplastic splenitis; rheumatic nodule in mitral valve; edema of lungs; hyperplastic adenitis of abdominal lymph glands.

For the purpose of orientation a few remarks on the nature of periarteritis nodosa may be inserted at this point. Periarteritis nodosa is probably not a disease *sui generis* but a hyperergic defensive reaction of the small muscular arteries and arterioles to a variety of releasing toxic and infectious factors. The relative simplicity of the histological structure of arteries results in a rather specific lesion being precipitated by non-specific factors; minor differences in structure, the location and existence of the vasa vasorum, and perhaps of the periadventitial lymphatics probably accounts for the location of the initial lesion and, in part, the type of response. At any rate the hypersensitivity induces an anemic necrobiosis of the medial muscle fibers, the coagulative and hyaline necrosis extending toward the intima and adventitia. Fibrinous and cellular exudation follows and granulation tissue forms. Intimal injury leads to thrombosis and endothelial or subintimal proliferation, to narrowing or occlusion of the vessel lumen with ischemia, infarction and nutritional disturbances in the organ supplied. Or, with persistence of arterial pressure, intimal necrosis, medial hyalinization, and destruction of the elastic lamina, mural tears, false aneurysms, rupture and hemorrhage results. Finally, replacement of the granulation tissue by indifferent fibrous tissue, canalization of the thrombi and perivascular scarring may result in "healing." Apparently the smaller vessels tend to thicken and the larger to rupture.

While periarteritis nodosa has been reported in an infant two and one-half months old and repeatedly in the seventh and eighth decades of life, more than one third of the cases are in the twenty-one to thirty-year period. Approximately 67 per cent of the cases occur in males. As a rule the past history

is singularly free from previous illnesses, although a history of a recent sore throat, "grippe," or upper respiratory tract infection occurs with suspicious regularity; undue exertion and exposure to inclement weather is not unusual. The recent preceding illnesses may have been regarded as trivial and perhaps would have been recorded more frequently if a special search had been made for it. The age, sex, and previous history in this case is illustrative.

Comparatively little is known about the true course of the disease since, until relatively recently, attention has been focused upon obscure and fatal cases. While a division into acute (death in a few days), subacute (death within five months), chronic (year-long duration or recovery) is didactically useful, the impression that a vast majority of the cases terminate fatally within a few months is not necessarily correct. The attempt to create clinical types, for example, gastro-intestinal, renal, neuromuscular, cardiac, cerebral and cutaneous forms, has resulted in some misunderstanding. The disease may remain localized to a single artery, for example, the hepatic or renal, but more commonly various vessels are simultaneously or sequentially affected. Moreover, a patient presenting neuromuscular involvement may suddenly develop a bronchitis, perforation of the intestine, or rupture of a renal artery with an immediate change in the entire clinical picture. This bizarre feature must be emphasized for a false impression could easily be created if one attempted to apply strictly the generalizations which follow in the symptomatology. Any symptom may be present; none are compulsory.

In regard to general impressions, a considerable number of these patients at first are suspected of having an infectious disease. The existence of fever, leukocytosis, tachycardia, increased sedimentation rate and changes in the albumin-globulin ratio support this impression. For this reason trichinosis, rheumatic fever, miliary tuberculosis, and typhoid fever are frequently encountered as erroneous diagnoses. The gradually progressive anemia, the pallor, marked loss of weight and strength may be striking because well-developed and well-

nourished males apparently in complete health are frequent victims. The presence of a syndrome suggestive of subacute sepsis should therefore induce consideration of periarteritis nodosa when an etiological diagnosis cannot be confirmed.

Fever is present in more than two thirds of the cases. Moderate elevations are encountered most commonly and they are often interrupted by afebrile episodes lasting one or more weeks. Recrudescences may be associated with local recurrences of the lesion, extension of the process, complications, or the appearance of skin nodules. The temperature curve does not conform to any particular type, but great irregularity and prolonged spontaneous remissions are suggestive.

The pallor is usually out of proportion to the severity of the anemia; circulatory changes may be partly responsible. Loss in weight and strength, and a cachectic appearance is fairly constant and often marked. Some authors attribute it to an endocrine (adrenal) component.

Recurrent punctate hemorrhages in the skin, at times generalized, and associated with joint pain and swelling are not unusual. This eruption may be accompanied by urticaria. Occasionally lesions resembling erythema nodosum and erythema multiforme may be noted. Nodules may form in the skin, then break down, and form shallow ulcers which heal slowly and recur. In many instances marked involvement of the skin has been associated with a benign course suggesting an esophylactic function of this organ.

Subcutaneous nodules vary from the size of lead shot to a hazel nut. They occur early or late in the course and their appearance is often associated with a recrudescence of fever. Rarely have more than 50 been encountered. At times they are sensitive, soft and elastic. They may disappear within thirty-six hours or persist for years, in the latter instance becoming hard. A careful search should be made for them since it is only by biopsy that the diagnosis may proceed beyond the presumptive stage. Owing to the fact that biopsy is usually performed on the suspicion of trichinosis, most nodules have been reported on the lower extremities. However they

may occur on any part of the body and in one case they were noted on the tongue.

Polymyositis occurs in more than half of the cases; drawing, tearing cramplike pains aggravated by active and passive movement and associated with pressure-sensitive muscles in the neck, shoulders, back, arms and legs is a very common mode of onset. While intermissions occur, muscle involvement usually persists leading to marked weakness and, at times, to decided atrophy of the muscles. When polymyositis is marked, there may be an edema of the overlying skin.

As in this case, the onset may be characterized by pain and swelling of the joints so that rheumatic fever is suggested. Mono-articular involvement is unusual. Salicylates do not seem to affect the symptoms nor the course of the disease.

In contrast to the rarity of central nervous system involvement, the peripheral nervous system is commonly affected. In regard to the former, the brain (and cerebral meninges) rather than the cord reveals the lesion. Isolated cranial nerve paralyses (oculomotor), cerebral hemorrhage and meningism or meningitis may be evident. The polyneuritis is very suggestive from a diagnostic standpoint. Median, radial, tibial or peroneal neuritis may be encountered, and a variety of paresthesias and hyperesthesia may occur. The nerve trunks are often sensitive. While ataxia and tremor do not occur, atrophy, hypotonia, and disturbances of motility are often evident. The tendon reflexes are diminished or abolished. At postmortem, the arteries of the nerves may or may not be affected.

In general the special senses are spared; this is rather surprising since one might expect considerable diagnostic assistance from the eyegrounds. At times blurring of vision is noted and edema of the retina and disk may be seen. When renal lesions occur, and they are perhaps the most constant feature of the syndrome, eyeground findings indistinguishable from ordinary albuminuric retinitis are noted. Marked retinal arteriosclerosis, arteriovenous compression, hemorrhages and "cotton wool" spots are frequent. Vertigo has been recorded

in connection with intracranial aneurysm; the ear seems to escape although bone involvement has been recorded.

The oral cavity, throat and larynx are seldom affected although the nodules have been noted on the tongue. A history of sore throat recently antedating the onset is common. In rare instances muscle involvement has led to disturbances of speech and swallowing.

Although periarteritis nodosa affects the bronchial arteries and pleura, decided respiratory symptoms are usually absent except for bronchitis, pleural effusion and pulmonary edema, which are noncharacteristic and together with pneumonia, are manifested as preagonal phenomena. The predominance of respiratory symptoms and resemblance to pulmonary tuberculosis is rare but not unique to this case. Bloody sputum and chest pain have been prominent features in some cases. It should be added that pulmonary infarction in these cases is usually not recognized and that the pleural effusions and subserous pleural hemorrhages more often are combined with the terminal uremia than with inflammatory processes in the lungs. Bronchial asthma is often recorded in the previous illnesses.

In view of the high incidence of periarteritis nodosa of the coronary vessels it is rather remarkable that cardiac symptoms do not play a greater rôle in the average case. Subjective complaints are not prominent although rarely an anginal syndrome may dominate the picture. Palpitation is an occasional complaint. Dyspnea is common but not characteristic. When prominent it tends to appear late in the course and is associated with left heart failure and the signs of uremia. Cyanosis is usually preagonal. Cardiac edema has been reported but the more common generalized and often transient edema seems to be of renal origin. Cardiac hypertrophy and dilatation are frequently noted. Concomitant endocarditis as well as functional insufficiency may be responsible for the variety of murmurs heard over the apex and base. The murmurs associated with relative insufficiency appear and vanish from time to time without apparent change in the circulation.

The electrocardiogram may reveal changes suggestive of myocardial involvement. It is probable that, perhaps, daily electrocardiograms would aid considerably in the differential diagnosis. At least, changes indicating alterations in the myocardial blood supply, while not peculiar to periarteritis nodosa, do not seem to occur in the diseases with which it is commonly confused. Cardiac irregularities are encountered in rare cases. A pulse rate disproportionately rapid for the temperature is quite suggestive of the lesion and may assist in differentiating it from typhoid. While changes are found in the vagus endings the myocardial changes would seem to be sufficient to account for the tachycardia. In recent years it has become increasingly evident that hypertension has been a seriously neglected symptom. At any rate the occurrence of a rapidly increasing hypertension in the course of a subacute febrile syndrome is peculiar and suggests periarteritis nodosa. It may be worthwhile to stress once again the variability of the picture. Sudden death from intrapericardial hemorrhage due to coronary aneurysm is known in periarteritis nodosa. Likewise instances of gradual cardiac failure have been recorded. Between these two extremes graded transitions occur.

The extreme variations of onset and course is demonstrated even more clearly by the renal involvement. Both extremes are fairly common, namely, sudden onset with massive fatal hemorrhage into the perirenal tissues producing an acute catastrophe, and the gradual development of a true chronic uremia. On the other hand, repeated smaller perirenal hemorrhages are reported as well as an onset with acute convulsive uremia. In addition to the symptoms mentioned above, such as transient edema of the face and extremities, hypertension, etc., evidence of a nephritis is one of the most constant clinical features of the disease while renal infarction is the most common pathological finding. The interlobular arteries are most often involved but in infarction the glomeruli may be affected. Albuminuria is a fairly constant feature of the syndrome; hyaline and granular casts, red blood cells are

found in the urinary sediment. Early, the urine may be scanty when marked sweating is present; later, the total amount falls and the specific gravity tends to become fixed. Simultaneously the phenolsulphonphthalein output falls and the blood chemistry reveals signs of increasing retention. While gross blood in the urine and symptoms suggestive of renal colic are recorded, the renal infarcts are relatively silent. Periarteritis nodosa not infrequently involves the vessels of the pancreas and glycosuria as well as changes in blood sugar may be noted.

Infarction of the testes has been observed occasionally. Complete absence of abdominal symptoms, as in this case, is uncommon. Since periarteritis nodosa affects the gastric, mesenteric, and intestinal vessels in most cases, some symptoms, even if they are not characteristic, are generally present. More than one third of the patients complain of nausea and vomiting; anorexia is even more frequent. About one half of the patients report abdominal pain which may be sufficiently severe to suggest an acute surgical abdomen. In several instances laparotomy has been performed early in the case on the presumption of an acute appendicitis. Save in one instance, the true lesion has not been diagnosed during abdominal surgery. Since infarction of the gastric and intestinal lesions usually results in erosion and ulceration of the mucous membrane and, moreover, since the ulcerations tend to perforate, operation is also performed late in the course of the disease. In a respectable number of cases signs of peritonitis were not manifest during life but a ruptured viscus was found at postmortem. This was suspected in this case when turbid fluid and a dull peritoneal surface were found at autopsy. However, examination of the microscopic sections failed to reveal an actual peritonitis and nothing was found except intense congestion of the entire gastro-intestinal tract.

Pain is usually upper abdominal; in order of frequency it is of epigastric, right and then left hypochondrial localization. Ordinarily the pain is cramplike or colicky in nature. Having appeared, persistence for weeks or months is the rule. Upon palpation, the entire abdomen may be sensitive and some-



what distended. Nodules have been felt in the abdominal wall. At times there is no tenderness in spite of severe pain. Vomiting may precede, often accompany and occasionally temporarily relieve the pain. When intestinal mucous membrane erosion exists, diarrhea and bloody stools are noted. Constipation is about as frequent as diarrhea and the two states may alternate.

The difficulties encountered in correctly appraising the abdominal symptoms are suggestive of the obstacles met universally in this syndrome. Intestinal symptoms may be marked and no lesions found to account for them at post-mortem, marked alterations in the intestinal vessels are also noted with no symptoms having existed during life; finally, the intensity of symptoms may parallel the pathology.

The cystic artery is frequently involved; it may be the first artery affected or at least provocative of symptoms. Inspection of the gallbladder during operation may reveal gross pathology although the true pathology is not realized by the surgeon and usually not by the pathologist until the gallbladder is restudied at the subsequent postmortem. In the syndromes of cholecystitis and dyskinesia of the gallbladder jaundice may be a prominent symptom.

Multiple infarction of the liver is extremely common; it may be partly responsible for some of the hypochondrial pain. But, like infarction of the spleen which also occurs frequently, the hepatic and splenic lesions are usually not suspected. Fairly often the spleen is palpable; although the liver is enlarged in about 25 per cent of the cases, the enlargement is usually not suspected during life.

The superficial lymph nodes are palpable in a respectable number of cases. However, the discrete, noninflamed, painless adenopathy is only moderate and diseases of the lymphatic apparatus rarely come under consideration in the differential diagnosis.

"Chlorotic marasmus," listed by older writers as a cardinal feature of the syndrome, was evident in this case. The hemoglobin is reduced quite regularly and, in most cases, last-

ing more than a few months, the red blood cells reach a level near 3,000,000. Exceptions to this general rule are not infrequent; profuse diarrhea and sweating may retard the appearance of the secondary anemia while massive bleeding or recurrent hemorrhages may accelerate it. In spite of the coexistence of quadrilateral paresthesias and achylia (anacidity or subacidity having been recorded in the few cases in which gastric analysis was done) pernicious anemia is rarely confused with periarteritis nodosa.

The white blood cell count may be normal but usually a moderate leukocytosis exists. Counts of 60,000 have been recorded; more than 30,000 are not unusual but figures near 20,000 to 25,000 are most common. Case histories often provide the impression of a leukocytosis out of proportion to the activity of the "infection," even if it harmonizes with the gravity of the clinical picture. The white blood cells also show a shift to the left. As a rule abnormal forms are not encountered but as high as 10 per cent myelocytes are recorded in the literature. Confusion with diseases of the hematopoietic system does not seem to occur.

An extremely interesting finding is the eosinophilia occurring in about 10 per cent of the cases. As many as 80 per cent eosinophiles have been encountered. This eosinophilia in association with markedly tender calf muscles makes trichinosis the first disease ordinarily considered; but the correct diagnosis is often obtained by muscle biopsies for suspected trichinosis. The eosinophilia occurs in the "absence" of other allergic phenomena such as bronchial asthma and urticaria and seems independent of the type of cellular exudate in the lesion.

In spite of the frequency of purpura, not many platelet counts seem to have been made. Increases as well as decreases have been reported.

Clinical pictures suggestive of sepsis prompt the procurement of blood cultures. Generally speaking these are negative although a variety of micro-organisms, usually streptococci, have been recovered in a minority of cases. Inability

to discover the etiology of an alleged sepsis together with negative blood cultures is suggestive of periarteritis nodosa. Positive blood cultures may lead to premature establishment of an erroneous diagnosis unless it is recalled that periarteritis nodosa may be a nonspecific vascular reaction occurring in conjunction with numerous infections. Gonococcal infection in a few instances seemed to possess etiological significance.

While syphilis is no longer regarded as exclusively responsible it may be an occasional releasing factor. The blood and spinal fluid Wassermann reactions are usually negative; causal connection may not exist even when they are positive. Institution of specific therapy in the syphilitic has occasionally coincided with the onset of the syndrome. Likewise antiluetic therapy alone or in conjunction with x-ray in rare instances was coincident with abatement of periarteritis nodosa. However, temporary spontaneous remissions are quite characteristic of the syndrome. Since with few exceptions only the fatal cases have been well studied and instances of spontaneous recovery have multiplied ever since clinicians became interested in the lesion, it is highly probable that our notions about the mortality are wrong and unrecognized cases with spontaneous recovery may be common.

While the protean character of the syndrome makes brief summarization rather futile, attention to the common clinical features such as inexplicable fever, polyneuritis and polymyositis with muscle atrophy, weakness and emaciation, persistent abdominal colic, edema and hypertension, purpuric eruptions and subcutaneous nodules will facilitate diagnosis, which may often be confirmed by biopsy. Most mistakes are made by not considering the lesion as a diagnostic possibility.

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### THE HORMONAL TREATMENT OF ACNE VULGARIS

ACNE is undoubtedly the commonest skin disease of the second and third decades of life. It is estimated that acne patients constitute about 8.5 per cent of all cases seen in dermatologic practice.<sup>1</sup> Its cosmetic importance, however, and its social, economic and psychological implications far outweigh its position as a trivial dermatosis, and bring it to the very forefront of major dermatological problems. Bloch's<sup>2</sup> summaries of the results of the examination of 4191 children between the ages of six to nineteen years, of both sexes, show that if we consider the comedo the essential lesion of acne, a few such lesions occur in an amazingly high percentage (64 per cent in this series). The percentage of individuals suffering from acne increases with age, and reaches its maximum in the seventeenth year for girls, and the eighteenth year for boys; only 3.4 per cent of girls in that group and 0.6 per cent of boys were entirely free from the eruption.

On the basis, then, of the above figures alone, it would seem that the development of a few acne lesions at the age of puberty is physiologically normal. It is only when the lesions are unusually numerous, severe, or persistent that we can consider acne a disease.

**Etiology.**—Many attempts have been made to approach the problem of the etiology of acne chemically, metabolically and by histological and bacteriological methods, with, however, little success. On clinical grounds it has long been suspected that acne vulgaris is caused by some endocrine disturbance, presumably by disturbance of the gonads, and many

observers have commented on it. Hollander<sup>3</sup> was impressed by the correctness of the conception that the underlying etiologic factor in acne is somewhere in the domain of the endocrine glands, probably the gonads; according to Schamberg,<sup>4</sup> when the phenomenon of the relapse during menstruation in persons with acne is considered in conjunction with the initial onset of acne at the approach of puberty, the inference appears to be justified that an internal secretion from the sex glands plays an important rôle. Darier<sup>5</sup> stated that localized acne of the chin in young women is supposed, almost certainly, to indicate utero-ovarian trouble.

Cunningham and Luntsford<sup>6</sup> conducted an interesting investigation among women college students, comparing 2974 girls with acne, with 3185 who did not have acne as controls. No difference was found in respect to the incidence of common disorders, such as constipation, incidence of colds, state of nutrition as expressed by weight, or conditions of the nose and throat, to which a contributory influence on acne is usually ascribed. No relationship between the presence or absence of acne in the fifteen to thirty-four year age group, and such menstrual characteristics as age of onset, duration, irregularity in interval, amount of pain and flow was demonstrated; thyroid enlargements were found to be associated with a slight increase in acne incidence. In connection with this last finding, it is of interest to note the possibility expressed by Sulzberger<sup>7</sup> and his co-workers, that increased thyroid activity, frequently coincidental with increased gonad activity and leading to increase in circulating thyroxin (the iodine-containing hormone) might explain acne vulgaris as essentially of the same nature as a very chronic iodide acne. Attempts to prove this experimentally by means of thyroxin patch tests did not, however, lend strength to this possibility.

The work of Stokes and King,<sup>8</sup> in demonstrating that there is a familial and heritable element in predisposition to acne vulgaris is significant, and important in prognosis and treatment.

The late Bruno Bloch<sup>2</sup> called acne, among other diseases, a

dyshormonal dermatosis. He noted the fact that eunuchs are said to be immune from acne, and that there have been pathologic cases in which acne appeared in the first years of life when (owing to suprarenal tumor) sexual maturity was precociously developed. In a series of interesting tables and graphs showing the correlation of acne, on one hand, and the commencement of the menses and the appearance of pubic and axillary hair, on the other, he demonstrated clearly that in any age group those sexually developed show a higher percentage of acne than those not sexually developed.

It was Bloch's opinion that acne in its first phase is a consequence of the physiological function of the sex glands, analogous to that which in general we assume for the development of the normal secondary sexual features, such as the formation of terminal hair. The degree of their formation is undoubtedly different. This may be dependent on the fact that the production of sex hormone is varied in strength in each individual, or (and this seems more likely) that the follicular apparatus of the skin (the receptor mechanism) is individually different in its sensibility to this hormone (as for example the type of beard varies in different men). As a result, we are faced by the fact that in acne the normal physiological action of a ductless gland—the sex gland—in the skin leads through transition stages to a final effect which is pathological—a real lesion of the skin, namely acne.

Anatomically, the first changes in acne are a follicular hyperplasia and hyperkeratosis, which is part of the general activation of the pilosebaceous system occurring in puberty. There is usually an accompanying increase in sebaceous secretion. Few patients remain in this stage; most go on to follicular infection and inflammation.

**Clinical Investigations.**—Until recently there was no means of demonstrating exactly the variations from the normal of the function of any sex gland. The newer knowledge of ovarian function, however, has provided a fairly precise method of determining the excretion of estrogenic substance in blood and urine, both qualitatively and quantitatively.

This was initiated by the studies of Stockard and Papanicolaou,<sup>9</sup> Evans and Long,<sup>10</sup> and Allen,<sup>11</sup> and depends on the fact that synchronously with the cyclical changes that take place in the ovaries, there occurs a cyclical change in the uterus and vagina of the animals used, and that the vaginal secretions partake of this change. The estrogenic substance is concentrated by lipoid extraction of the blood or urine. It is unnecessary here to go into detail regarding the principles and technic of its isolation and recognition. In our work the method described by Kurzrok and Ratner<sup>12</sup> was used for extracting the hormone from the urine, and that of Frank and Goldberger<sup>13</sup> for extraction from the blood. The vaginal spread of the castrated rat is used as indicator.

For the sake of completeness, although the author has had no experience with it, some mention will be made of the testis hormone. This was recognized by McGee<sup>14</sup> in 1927 in lipoid extracts of the testes. The test for the testis hormone is not as clearly defined, and is slower than that for estrogenic substance in the female, and is accomplished by means of the capon test (comb, wattles and spurs).

It is important, at this juncture, to emphasize the discovery, by Smith<sup>15</sup> and shortly after by Zondek and Aschheim<sup>16</sup> that both ovary and testis remain dormant unless stimulated by the secretion of the adenohipophysis (anterior pituitary or pre-pituitary gland) and that this gonadotropic factor activates alike the gonads of both sexes.

It was thought that evidence of normality of ovarian function would be indicated by a study of the excretion of estrogenic substance in the urine and blood of patients with acne. Kurzrok's<sup>17</sup> studies have shown that normal women between the ages of sex maturity and the menopause excrete from ten to twenty rat units of estrogenic substance per liter of urine throughout the menstrual cycle.

The urines of 34 young women who applied to the Vanderbilt Clinic for treatment of acne were examined. The age range was eleven to thirty-three years, 21 being under twenty years of age.

The results were as follows:	Number of patients	
Strongly positive reaction (10-20 rat units) . . . . .	6	} 82 per cent
Slightly positive (4 rat units) . . . . .	1	
Negative reaction . . . . .	27	

In the blood, the work of Frank and his associates tends to show that in the normal fertile menstruating woman the concentration of estrogenic substance undergoes regular cyclic variations, and also that the renal permeability to these substances varies in the individual. In view of these possibilities it seemed desirable to repeat the above observations, estimating premenstrual values for estrogenic substance in the blood of patients with acne.

In normal fertile menstruating women Frank and Goldberger found one mouse unit of estrogenic substance in 40 cc. of blood taken from the tenth to the third day premenstrually in 44 per cent of their patients, while from the third to the first day premenstrually at least one mouse unit was present in the blood of 100 per cent of the patients. (Average for the entire period 72 per cent.) Neustaedter<sup>19</sup> found estrogenic substance in the blood of 75 per cent of his patients in a similar interval; Mazer and Goldstein<sup>20</sup> found the percentage slightly higher in their series (85 per cent).

With these figures representing average norms, we may compare them with the findings in normal menstruating women with acne. Twenty-nine consecutive patients with acne with normal menstrual histories were examined. In none of the patients studied were any other acne-producing factors, dietetic or chemical, detected. Their ages ranged from eleven and one-half years to thirty-four years, and the menstrual interval ranged from twenty-one to thirty-one days. Forty cc. of venous blood obtained within seven days of menstruation was assayed for estrogenic substance by the method of Frank and Goldberger. The results were as follows:

	Number of patients	
Strongly positive reaction (1 mouse unit) . . . . .	2	} 93 per cent
Weakly positive (less than 1 mouse unit) . . . . .	16	
Negative reaction . . . . .	11	



**Results of Treatment.**—Van Studdiford<sup>21</sup> treated a number of female patients with acne with a variety of endocrine products, including desiccated ovarian extract, and orchic extract. More recently 15 patients were treated with estrogenic substance, three doses being given by injection on alternate days one week premenstrually. Of these patients, 11 improved. Sixteen patients in another series were treated with a preparation of gonadotropic substance postmenstrually, as a stimulative measure, followed by the injection of estrogenic substance premenstrually, as a substitutional measure. Eight of the patients treated in this manner showed improvement.

Michaels,<sup>22</sup> working in cooperation with gynecologists in order to employ the newer endocrine products in the most suitable manner, treated 26 acne patients with hormone therapy. The therapeutic results were poor, and discouraging so far as the influence of the hormone treatment on the acne was concerned.

Lawrence and Feigenbaum<sup>23</sup> treated 6 males and 8 females with pregnancy urine extract, with results sufficiently satisfactory to warrant further study. In a subsequent report Lawrence<sup>24</sup> treated a series of 30 patients in the same manner; 10 were regarded as cured, as they had had no relapse two months after treatment had ceased, while 11 were definitely improved.

The patients in my series number 38 females and 2 males, practically all of whom were followed for almost two years. The ages of the female patients ranged from thirteen to thirty-three years, the average age being nineteen and eight-tenths years. Physical examination, apart from the presence of acne vulgaris, was essentially negative in all, except for 2 patients who had pulmonary tuberculosis in arrested stages. One patient showed a basal metabolism rate of +35 per cent, although there were no clinical signs of hyperthyroidism. Seven of the patients were married.

An analysis of the menstrual histories of the patients studied failed to reveal any relation between the acne and any particular menstrual characteristic. A number of the patients

reported premenstrual aggravation of the eruption, while a few thought that it was better at that time.

Treatment consisted of 5 injections of 1 cc. each, of a preparation of estrogenic substance (50 rat units) given at daily intervals, followed by the same number and dosage of a pregnancy urine preparation (containing 100 rat units to each cc.) instituted postmenstrually. This amount of treatment was termed one course. After the next period, a similar course of treatment was administered. During this time no local applications or treatments were prescribed.

The 2 male patients, aged seventeen and eighteen years respectively, were given 1 cc. of pregnancy urine extract three times weekly for several weeks; one made a speedy and complete recovery, while the other showed no improvement.

The results of treatment of the female patients are as follows:

	Number of patients	Average number of courses per patient
Definitely improved	13	2.3
Slightly improved	10	1.8
No improvement	15	1.4

It is evident that the total amount of treatment administered bears a definite relation to the end-result, as the patients who improved received almost twice as much as those who did not (2.3 courses compared with 1.4).

In connection with this type of therapy, it is pertinent to call attention to the possible ill-effects attending prolonged treatment with estrogenic substances. Kunde *et al.*<sup>25</sup> in 1930 showed that continued high dosage of estrogenic substances has a distinctly sclerosing effect on the ovaries. Numerous reports have also appeared relating to the carcinogenic properties of estrogenic substances; one observer<sup>26</sup> states that mammary cancer developed in male mice following treatment with these substances, while others saw atypical growths, resembling cancerous changes in the uterine cervix of monkeys after prolonged treatment. Recent biochemical studies of Dodds,<sup>28</sup> and

Merrian,<sup>29</sup> among others, have demonstrated the close chemical and biological relationships between carcinogenic compounds and estrogenic substances; both contain a phenanthrene nucleus and possess the property of follicular irritation.

**Comment.**—The treatment of acne is still a problem, mainly as a result of uncertainty as to its cause; roentgen therapy, formerly regarded as a specific, has not proved completely satisfactory in all cases, although it is undoubtedly the best single and the most certain means of treatment available. McKee and Ball<sup>30</sup> obtained complete clinical cures in about 83 per cent of their cases with x-ray; Lord and Kemp<sup>31</sup> found about 75 per cent of their patients cured, and Michael<sup>32</sup> had final success in about 85 per cent of his patients with x-ray treatment. It is in the group of approximately 20 per cent of x-ray failures that one must consider an alternate form of therapy. It is the disappointing experience of every dermatologist to see relapses or recurrences in patients who have had maximal amounts of roentgen irradiation; among other forms, surely treatment with hormone preparations has a definite place.

It is believed that on the basis of the foregoing investigations one may assume that a definite relationship exists between the estrogenic hormone and acne, and that a deficient secretion of this hormone may prove to be the direct or indirect factor in the causation of one type of acne. While it is known that the anterior pituitary gland governs or regulates gonadal activity no information is available as to the apparent dysfunction, if any, in the link between it and the ovary. In this connection a possible, although remote, explanation of part of the improvement following roentgen irradiation may be attempted. It is conceivable that, in the course of routine roentgen therapy for acne, the pituitary gland is affected by the irradiation administered, and, in consequence, induces a normal gonadal response.<sup>33, 34</sup>

The evidence is strong, then, that one type of acne is caused by disturbance of the sex endocrines. Just what that disturbance is, or how it acts, is not clear. Endocrine therapy

for acne is not yet completely reliable because we do not know the best preparations to use, or how to administer them. At the same time in addition to any so-called "specific" therapy, an appreciation of the secondary factors involved in the management of any acne patient is very important; these have been clearly outlined by Wise and Sulzberger,<sup>35</sup> and need no re-emphasis here.

**Conclusion.**—Estimation of estrogenic substance in the urine and blood in two independent series of females with acne yielded parallel results: 82 per cent of patients showed absence or subnormal quantity in the urine, and 93 per cent showed absence or subnormal quantity in the blood.

This leads to the belief that associated with acne there is abnormality of formation or of utilization of the sex hormone. The exact nature of this aberration and the direction it takes are unknown. It is as yet undetermined whether lack of estrogenic substance or some other basic fault is the cause of acne.

Treatment of these patients with preparations of estrogenic substance and gonadotropic substance, as outlined above, produced some favorable results (60 per cent improvement). This may be compared with the results obtained with x-ray treatment, about 80 per cent.

Prolonged treatment with estrogenic substances is not without danger; sclerosis of the ovaries, and carcinogenesis have been reported.

The basic principles underlying the general management of patients with acne must not be overlooked, regardless of what specific therapy may be employed.

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TUBERCULODERMS

THE dermatologic manifestations of tuberculosis are diverse and protean. All are due to the effects of the tubercle bacillus, but it would, indeed, represent a great step backward to be content to call these many different and distinctive manifestations all simply "tuberculosis of the skin."

It is particularly the studies of Wolff-Eisner, and of J. Jadassohn, Lewandowsky, and Martenstein, and their school that have demonstrated that a large part of the variability in the morphea and the course of the various types of skin tuberculosis is dependent upon local immune-biologic alterations of response (allergy) on the part of the tissues of the host.<sup>1, 2, 3, 4, 5, 6</sup> Such fundamental immunologic studies on a dermatologic object inevitably bring to light basic principles applicable to resistance and infection in general. For example, there can be no doubt that further study of pulmonary and other internal tuberculosis will eventually demonstrate a similar influence of immunologic forces and possibilities of immune-biologic classification.\* These points are well illustrated in two excellent papers by Max Pinner, in the first of which<sup>7</sup> the question of the influence of allergy (*i. e.*, altered

\* Some of our recent immunologic studies on the tuberculoderms were made possible by a grant from The Hofheimer Foundation of New York City, and we take this opportunity to express our appreciation of this generous contribution.

responses) is discussed in relation to the course and immunity of pulmonary tuberculosis, and in the second of which<sup>8</sup> attention is called to a relatively benign and a-bacillary form of hematogenous nonmiliary pulmonary tuberculosis. It seems possible that some of the cases he describes are analogous to sarcoids; are, perhaps, actually isolated "sarcoid" disease of the lungs, appearing without skin sarcoids. It would be of interest to know the reaction of Pinner's 28 cases to intracutaneous quantitative tuberculin tests. We believe that in some, at least, such tests might possibly bring to light a specific anergy; and thus might practically establish the absolute immunologic relationship of the cases to Besnier-Boeck's disease and to the sarcoid forms of skin tuberculosis.

General considerations of this nature constitute, perhaps, the main reasons for preserving the knowledge that has already been gained; and for continuing to maintain the clearest possible distinction between individual tuberculoderms. In addition to general reasons, however, there is a more specific reason for interest in immune-biologic phenomena in relation to tuberculosis of the skin. A rational immunobiologic classification of value is possible not only because of definitions, terminology, and mutual understanding, but, also, because of the indications furnished for proper management and therapy, as well as for the determination of prognosis in the individual case.

It is the purpose of this contribution to resubmit—though only schematically and concisely—the classification of tuberculoderms that today enjoys the most widespread general acceptance, and which is essentially that of the Jadassohn-Lewandowsky school.

Since a division into various categories ultimately depends upon biologic, and particularly upon immune-biologic phenomena, it is self-evident that the lines drawn cannot have mathematical precision. There must be overlapping and transitional forms; exceptional and unclassifiable cases; and cases which seem to violate any and all rules. In spite of the exceptions, however, the classification offered has stood the test

of time, and has shown itself to be practically and theoretically indispensable.

Although many of the essential characteristics of the common tuberculoderms have been known for more than thirty years, nevertheless there still exists, unfortunately, not inconsiderable confusion in regard both to the concepts and to the terms forming the basis of a rational classification of skin tuberculosis.

Three points in particular seem to give rise to misunderstanding. The first of these is the meaning of the phrase, "*primary* tuberculosis of the skin," the second is with regard to the definition of "tuberculid," and lastly the loose employment of the words "tuberculous," "tubercle," "tubercular," and "tuberculoid."

*Primary tuberculosis of the skin* designates only those skin conditions which result when the tubercle bacillus invades the skin of an individual never before infected by this micro-organism, either in the skin or in any other organ. This occurs only when there is a first tuberculous inoculation of the skin in a person previously entirely free from tuberculosis.

Obviously, primary tuberculosis of the skin must occur predominantly in infants and young children, in whom there is less likelihood of an earlier pulmonary, gastro-intestinal, or other internal infection, and it is, therefore, relatively rare. It can occur only on areas exposed to external infection; and the bacilli causing the lesion must necessarily, directly or indirectly, emanate from some other host.

The two well-known representatives of primary skin tuberculosis are:

1. Massive infection in the very young infant (E. Wolff, G. Fedders, and others<sup>2</sup>) following ritual circumcision. This type of infection produces a rapidly growing ulcer, and frequently terminates fatally.<sup>9</sup> Fortunately, this form is almost an entity of the past.

2. A small, hard, indolent ulcer with marked, nontender regional lymphadenopathy—usually seen in children. The picture so closely simulates primary syphilis that it is usually



at first diagnosed as syphilis and it has, indeed, come to be known as tuberculous chancre or chancriform tuberculosis.<sup>10, 11, 12, 13, 14</sup>

All of the other forms of skin tuberculosis are not to be classed as *primary*, for they represent superinfection or reinfections in the immunologically altered skin of *previously infected* individuals (regardless of the site of the previous inoculation). This immunologic alteration of the skin persists in most instances, and is generally present irrespective of the state of activity or healing of the primary, internal or other focus. Therefore, no primary tuberculoderm can later occur in an individual who was at any time previously inoculated with the bacillus.

*Tuberculids*.—There are some who would place the words “tuberculosis” and “tuberculid” in sharp contrast to each other; would even make these two terms mutually and reciprocally exclusive. This is obviously impossible. All tuberculids are tuberculosis; just as all syphilids are syphilis; and just as all dermatophytids are manifestations of dermatophytosis. “Tuberculosis” is the inclusive term, and means simply a pathologic process due to the effects of the tubercle bacillus. “Tuberculid,” on the other hand, refers to certain skin manifestations of tuberculosis characterized by the presence of a group of fairly distinctive criteria.

To be termed a tuberculid, a manifestation must conform to the following criteria:

1. It must be secondary in the sense that it must be due either to bacilli or to the products of bacilli or to both, emanating from a focus elsewhere in the same individual.

2. It must differ somewhat in nature from the distant focus, this difference being largely attributable to the immunobiologic alteration of the tissue in which the tuberculid appears. But the tuberculid differs from the lesion of direct inoculation, not only because it appears at a later date in a skin already immunologically “prepared,” but also because it has an entirely different pathogenetic mechanism from that of

the primary lesion or of the exogenous local superinfection or reinfection.

There are further characteristics suggestive of an "id." Although an "id" may occasionally be lymphogenous in origin, or may arise even by contiguity, it is of *hematogenous* origin in the overwhelming majority of instances. Furthermore, "ids" usually appear in showers, symmetrically disseminated, and generally without constitutional symptoms. Moreover, the individual lesion of an "id" does not usually continue to grow greatly toward the periphery, but is confined to the original area or its immediate vicinity. In addition, it is very likely to heal spontaneously.

In many forms of tuberculids, the immunologic alteration manifests itself by causing either a very rapid destruction or attenuation of the bacilli which may have arrived at the site; the altered response of the tissues is further made evident by the altered histopathologic picture in which specific tubercle formation (*i. e.*, the formation of fully developed, characteristic tubercles) may be either in the background or entirely absent.

We wish expressly to emphasize that the concept "tuberculid" does not imply that the lesion has been caused by non-living bacillary products alone; and thus does not imply that no living organisms have been or are actually present at the site of the lesion. While it was originally believed<sup>16</sup> that living organisms were never present, and that "ids" were produced exclusively by the products of organisms, this idea was almost immediately proved to be erroneous, and was soon discarded.<sup>16, 17, 18, 19</sup> (See Goldsmith<sup>20</sup> for a discussion of theories concerning attenuated bacilli and filter-passing forms.) The concept of the purely toxic nature of any "id" is today entirely untenable, "for it has been proved time without number that living micro-organisms are demonstrable (at the proper time and with the proper technic) in practically all 'ids.'"<sup>21</sup>

Although the histologic structure of a tuberculid may contain typical tubercles (as, for example, in *lupus miliaris disseminatus faciei*), it may be merely tuberculoid (as in the

naked epithelioid tubercle of the sarcoids), or it may be, to a great degree, nonspecific (as in certain cases of tuberculosis indurativa and tuberculosis papulonecrotica); or the histology may present combinations of all these forms.

*Tuberculous* means "due to the action of the tubercle bacillus"; as in tuberculous disease, which includes any manifestations due to the mycobacterium tuberculosis; tuberculous tissue thus meaning the tissue found in any type of tuberculosis.

*Tubercle* is an anatomicopathologic concept which, unless qualified, refers only to the typical, fully developed, mature tubercle; and does not refer to actual etiology or genesis. The typical mature tubercle is considered to consist of central caseation, epithelioid cells, and giant cells; and a surrounding lymphocytic wall. This structure is found most often in tuberculosis, but it may occur, exceptionally, in other so-called "chronic granulomas" such as syphilis, leprosy, sporotrichosis, etc., or even as the result of the deposit of nonliving substances in the tissues (tuberculin, trichophytin, oidiomycin, Frei "vaccine," etc.).

*Tubercular* means "characterized by tubercles."

*Tuberculoid* designates either: (a) structures not actually typical tubercles, but which resemble tubercles to a certain degree; or, (b) resembling the disease tuberculosis. In the former sense, it is strictly a morphologic and histopathologic concept; so, for example, the groups of epithelioid cells without caseation and with little or no lymphocytic reaction, as seen in sarcoids, are called "tuberculoid" structures.

Even with the closest possible adherence to the concepts and definitions outlined, the classification of the tuberculoderms is not simple, and, since we have not seen a concise tabular presentation in an American text, it would seem to serve a useful purpose to set forth a classification of the most important forms of skin tuberculosis as simply as possible.

In the table presented herein, which is derived from the classic tabulations of Lewandowsky,<sup>1</sup> Jadassohn<sup>3</sup> and Martenstein and Noll,<sup>4b</sup> no attempt is made to describe the various tuberculoderms or to elucidate many of the points of differen-

tial diagnosis. We have endeavored merely to bring out that this grouping of the various forms is based upon three main factors: (1) the immunologic status of the skin; (2) the resultant clinical and histological morphe and course; and (3) the immunologically determined bacteriologic findings. All statements, particularly those applying to the tuberculin test, express exclusively the *average* findings which become evident only through careful study of large series of cases. They do not apply to small groups, and still less to individual cases; nor do they take into consideration the many exceptions and the aberrant findings in a constant representative minority of cases. Biologic rules cannot be rigorously applied; they can be regarded only as indices of basic, wide, and important trends.

We believe that a study of the table, which indicates a possible correlation between tuberculin response, type of histologic reaction, and bacteriologic findings, must make it evident that the immunologic mechanisms, including hyperergy and hypoergy, are important determinants of the form and course of tuberculosis of the skin.

If this be true, it is logical to assume that, in a given case, factors producing alteration in the immunologic response of the skin to tuberculin might also exert a decided influence upon the existent tuberculoderm. In many instances, this assumption has actually been proved, and specific hyposensitization of the skin, by means of repeated intracutaneous injections of tuberculin in gradually ascending doses, has shown itself to be of decided therapeutic value.

We, ourselves, have achieved indubitable—sometimes even astonishing—results through the employment of this method in cases of hyperergic forms of skin tuberculosis, such as rosacea-like tuberculids, certain cases of tuberculosis papulonecrotica, tuberculosis indurativa, and in some cases of lupus vulgaris.

Undoubtedly it is not only of practical, but also of the very greatest theoretic interest that, by means of carefully graduated, repeated intracutaneous injections of ascending doses of

A SCHEMATIC CLASSIFICATION OF SOME OF THE IMPORTANT TUBERCULODERMIS \*\*\*

Name.	Mode of infection	Clinical appearance, course and sequelae.	Histologic structure.	Demonstration of bacilli.	Tuberculin reaction as determined by quantitative intracutaneous testing (based on Martenstein and Noll's and our own observations).
I PRIMARY TUBERCULODERMIS: A. <i>Tuberculous ulcers—very young infants</i>	Exogenous, heterogeneous, often after injury.	Rapidly growing ulcer sometimes with regional adenopathy. Often toxemia, then septicemia and death.	Basal inflammatory reaction.	+++++	Usually negative. (Very few cases tested.)
B. <i>Tuberculous chancre—usually in young children.</i>	Exogenous, heterogeneous, often after injury.	Small, hard, indolent ulcer with regional nontender adenopathy. The ulcer may heal or may lead to lupus vulgaris or scrofuloderma or some other form. The regional glands may become calcified.	First banal, later tuberculoid.	+++	First negative, later ++++ or +++++ as in lupus vulgaris.
II SECONDARY TUBERCULODERMIS: A. <i>Hypertrophic forms with peripheral extension.</i> 1. Tuberculous lupus (lupus vulgaris, and as a subgroup, hematomatous lupus vulgaris)	Usually autogenous and external or by extension from mucous membranes. May be lymphogenous or hematogenous (postextrematic form—hematomatous lupus vulgaris).	Papular infiltrations, apple jelly nodules, peripheral extension, destructive scarring, chronic course. Often on face, but may occur at any site.	Tuberculoid (usually no central caseation).	++ (with some difficulty—usually only by means of animal inoculations).	+++++ (strongly hyperergic).
2. Tuberculous verrucosus (anatomic tubercle, verrucous necrogena).	External in almost all cases. Autogenous or heterogeneous often after injury.	Usually on hand, extremity. Hyperkeratotic warty lesion, chronic course, little peripheral growth. Sometimes accompanied by lymphangitis and adenitis. Healing with scarring.	Tuberculoid structure mixed with banal inflammatory reaction (no caseation, but supuration is sometimes present).	++	+++++ (strongly hyperergic).
3. Tuberculous colligativa or chloasma.	Lymphogenous or by direct extension from soft tissue, bones or lymph node.	Fluctuating "cold abscesses," sinuses, etc. Usually spontaneous healing with scarring.	Tuberculoid with a large amount of banal inflammatory reaction and suppuration.	+++	++++ (hyperergic).

B. *Hyperergic forms without peripheral extension (usually hematogenous and generally called tuberculoid).\*\*\**

1. Tuberculosis lichenoides (lichen scrofulosorum)	Hematogenous.	Grouped follicular lichenoid papules. Spontaneous healing without scarring.	Tuberculoid (no caseation).	+ in very early lesions; difficult of demonstration particularly in fully developed lesions.	++++ (strongly hyperergic).
2. Rosacea-like tuberculoid	Probably hematogenous.	Rosacea-like appearance: papules, sometimes pustules and cysts with some telangiectasia. Location: face, forehead, sometimes neck and chest. Chronic course. Little scarring.	Occasional tuberculoid structure. Otherwise similar to acne rosacea except for less suppuration and less strictly follicular or perifollicular.	Not accomplished.	++ ++ (strongly hyperergic)
3. Tuberculosis papulonecrotica (papulonecrotic tuberculoid, acne, follicles, etc.).	Hematogenous. Rare cases are lymphogenous.	Mainly on legs, arms and buttocks in young females, often with certain constitutional anomalies and with vascular dysfunction. Papules with round crusting or necrotic central ulcer. Depigmented scars with hyperpigmented margins. Spontaneous healing.	Tuberculoid, but with many areas of banal inflammation and necrosis. Superficial.	Very difficult but can be accomplished from the early lesion by numerous biopsies and guinea-pig inoculations.	Approaching anergy: A relatively large number of cases show reduced sensitivity, while some are very strongly hyperergic.
4. Tuberculosis indurativa (erythema induratum of batin).	Hematogenous.	Mainly on legs in young females of similar type as those with tuberculosis papulonecrotica. Large, soft, bluish lesions breaking down to ulcers. Spontaneous healing with scarring.	In the deep cuts and throughout the fat. Shows perivascularitis. Otherwise like tuberculosis papulonecrotica.	As in tuberculosis papulonecrotica.	As in tuberculosis papulonecrotica.

\* We are greatly indebted to Dr. H. E. Mohr for his criticism and for helpful suggestions in the preparation of this table.

\*\* This tabulation has been deliberately abbreviated to exclude many rarer forms, such as military ulcerative tuberculosis (often postexanthematic and due to a so-called "negative or nonspecific anergy"), ulcerative tuberculosis of the face, tuberculous fungosa et serpinginea of J. Jadassohn, etc. The object throughout has been simplification and condensation, since we are endeavoring to present a simple and workable rule-of-thumb arrangement for the student, rather than an all-inclusive and absolutely correct, but thereby necessarily complicated and confusing tabulation.

\*\*\* We wish to emphasize again that the concept "tuberculoid" is not to be juxtaposed to the concept "true tuberculosis." Tuberculids are forms of tuberculosis presenting certain distinguishing characteristics. Tuberculids are not necessarily devoid of living organisms, nor are typical tubercles necessarily lacking. While the concept "tuberculoid" cannot be considered a strictly scientific one, it is nevertheless fairly well defined; it is of great value; and it seems essential that it be retained.

A SCHEMATIC CLASSIFICATION OF SOME OF THE IMPORTANT TUBERCULODERMS (Continued)

Name.	Mode of infection.	Clinical appearance, course and sequelae.	Histologic structure.	Demonstration of bacilli.	Tuberculin reaction as determined by quantitative intracutaneous testing (based on Mantoux and Nolté and our own observations).
C. <i>Relatively anergic forms (also considered as tuberculids).***</i>					
1. Lupus miliaris disseminatus (faciei)	Hematogenous.	Bluish-red, pinhead- to large pea-sized nodules with typical central apple-jelly appearance, central necrosis, or apparent central pustulation. Usually confined to face, and often on eyelids. Chronic course. Heals with slight, often varioliform scarring.	Fully developed tubercles.	Extremely difficult, but has been possible in some cases. <sup>22</sup>	Usually less sensitive than the normal; i. e., relatively anergic to tuberculin. But some cases are strongly hyperergic. This disease, in our opinion, forms the possible transition from tuberculosis papulonecrotica and tuberculosis indurativa to the sarcoid forms below. <sup>†</sup>
2. Sarcoid forms.					
(a) Sarcoid of Boeck.					
(b) Sarcoid of Darier-Roussy.	Probably hematogenous or lymphogenous.	Superficial (Boeck) and deep (Darier-Roussy), bluish-red, torpid, benign nodules little or no tendency to break down. Scarring not severe, but sometimes atrophic scars result. Not infrequently part of generalized sarcoid disease (Boeck-Benier's benign miliary sarcoid), which includes alterations in the lungs (miliary sarcoid infiltration), spleen, liver, etc. There are also cystic changes in the bones, usually in the phalanges (osteitis tuberculosa multiplex cystoides of Juengling). Prognosis of these forms is good.	Tuberculoid, i. e., naked epithelioid cell tubercles with no central caseation and little or no peripheral lymphocytic zone, lying between connective tissue septa.	Almost always impossible; successful only in rarest instances and in very early lesions or when transitions to other forms such as lupus vulgaris are taking place.	Usually much less sensitive than normal. This is the group with relatively excellent prognosis, and with so-called "postive, relative or specific tuberculin anergy" (in sharp contrast to the negative or nonspecific anergy found in military tuberculosis, postexanthematic ulcerative tuberculosis, and other forms, in all of which the prognosis is grave). <sup>†</sup> There is also said to be a high titer of tuberculin-neutralizing antibodies in the blood sera of these cases. <sup>20, 21, 23</sup>
(c) Angiolupoid, lupus pernio and other rarer forms are here considered as belonging to this group.					

† All reactions of this sarcoid form can occasionally be produced by other agents, living or dead. Sarcoid reactions are found occasionally in many chronic infections such as leprosy, tinea, syphilis, etc., and after injections of various extracts such as tuberculin, trichophytin, etc.

old tuberculin Koch, the skin of patients originally reacting to dilutions of 1:1,000,000 and greater, can eventually be brought to tolerate relatively high concentrations with little reaction; and that, concomitant with this demonstrated reduced skin sensitivity to tuberculin, there is, not infrequently, a noteworthy improvement or a cure of the tuberculoderm; and that, later, there is, in some cases, a return of the *original tuberculin hypersensitivity* coinciding with a recurrence of the *original tuberculoderm*.

It would be most misleading to imply that the tuberculoderms, as a whole, religiously follow a schematic outline; or that their manifestations are based entirely and solely on the degree of skin hyperergy or hypoergy. On the contrary, there are many contraindications and mysteries which still await clarification, some of which may be due to the fact that the data assembled have been gathered through technics literally replete with possible factors of error.

For example, in our investigation, we are employing dead tuberculin, which surely contain only a few of the allergens and properties of the living bacilli; and, in general, we have been attempting to study immunologic processes, often of incredible fineness and delicacy, with clumsy and inadequate tools. Moreover, our tuberculin tests are being applied in the wrong place, *i. e.*, distant from the actual site in whose immunologic status we are interested; and are also being applied at the wrong time, *i. e.*, long after the actual time at which the immunologic status determined the character of the lesion.

In view of these and other facts, it is not the many contradictions that are astonishing, but rather the degree of order and regularity which can be demonstrated by even such crude measures. It is to be hoped that with improvement in methods, such as, for example, the antigen analysis (W. Jadasohn) fractionation and purification of tuberculins, dermatology will penetrate much farther than it has as yet into the nature of the immunologic processes which are obviously such important factors in tuberculosis of the skin.



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## CLINIC OF DR. A. HYMAN

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### THE DIAGNOSIS OF MALIGNANCY OF THE URINARY TRACT

THE importance of early diagnosis in malignant disease of the urinary tract cannot be overemphasized. A careful study of over 1500 cases of malignancy of the genito-urinary tract, makes one realize that much too often the disease is seen by the specialist in an advanced stage of development. A number of factors no doubt contribute to this unfortunate state of affairs. In the first place, too many patients first apply for treatment late in the course of the disease. At times the patient cannot be held responsible for this. Only recently I operated on a patient with a large kidney neoplasm in whom the initial hematuria occurred within a month of the time when she first sought medical aid. On the other hand, our records show that in over 60 per cent of cases of tumor of the kidney, more than six months had elapsed after the primary hematuria, before surgery was resorted to. The significance of hematuria is undoubtedly underestimated both by patient and physician. Unfortunately, in renal and vesical neoplasms, the hematuria is painless, at times lasting only a day or two, and ceases spontaneously not to reappear for months. Such a course of events often fails to impress the patient or his physician with the potentialities of the situation, and months of valuable time are lost waiting to see if another attack of hematuria supervenes. Since the early diagnosis of malignancy of the urinary tract rests to a large extent with the practitioner who is first consulted, he should realize that hematuria is a symptom only

too often associated with serious disease of the urinary tract. The physician should impress upon the patient the importance of a thorough urological examination, to determine the exact source and cause of the bleeding.

### RENAL NEOPLASM

We have all been taught the textbook description of the three cardinal symptoms associated with renal neoplasm—pain, tumor and hematuria. Such a triad of symptoms generally denotes an advanced lesion, and under such circumstances the diagnosis presents no difficulties. Unfortunately, the symptomatology is at times so complex and protean in character, as to render the clinical picture most baffling. Not infrequently, there are few symptoms referable to the kidney and the first indication of a primary renal neoplasm may be the appearance of a metastatic lesion. We have found that the symptomatology of renal neoplasm may be classified under the following five types:

1. Hematuria.
2. Pain.
3. Tumor.
4. Gastro-intestinal and toxic manifestations.
5. Metastatic.

Hematuria is the outstanding symptom of renal neoplasm, and as an initial symptom was present in over 60 per cent of the cases, and during the course of the disease was present microscopically or macroscopically in over 90 per cent of the cases. Unfortunately, in some instances it is not always an early symptom. Occasionally it was noted only a few weeks prior to discovery of a large growth. The bleeding is painless in type, although the passage of clots down the ureter may produce colicky attacks of pain. Pain as an initial symptom may play an important rôle, as it often manifests itself before hematuria occurs. It was present initially in 30 per cent of the cases. The character of the pain may vary from a dull ache to sharp neuralgic pains down the back and thigh and is often described as lumbago or sciatica. Severe constant

neuralgic lumbar pains are often indicative of rupture of the growth through its capsule.

Tumor formation was present in almost 80 per cent of our cases, and its presence especially when associated with hematuria is of greater diagnostic value than other symptoms. Such a combination, however, generally denotes a lesion well advanced. Bimanual examination in the lateral position by displacing the kidney against the anterior abdominal wall, helps materially in detecting tumors otherwise not palpable. It is often impossible to differentiate a renal neoplasm from a splenic enlargement either by palpation, or by pyelographic studies.

Under the heading of general toxic manifestations, are certain symptoms such as loss of weight, cachexia and fever. These may be the first symptoms that point to a grave constitutional disturbance and in the absence of hematuria render the diagnosis very complex. As a rule, renal neoplasms do not produce the degree of cachexia so often seen in new growths of the intestinal tract. At times gastro-intestinal symptoms (anorexia, nausea and vomiting) dominate the picture giving the impression of a gastric neoplasm. These symptoms regarded as toxic manifestations due to absorption of the growth, often disappear immediately after nephrectomy. Fever is occasionally noted, probably due to a breaking down of the tumor, or infection. In over a dozen cases fever was noted without the presence of an associated pyuria. Israel, who first called attention to the fever associated with renal neoplasm, claimed the fever was not due to a necrosis of the growth, because the very large tumors in which we expect necrosis are not associated with fever, and in the tumors with necrosis fever was not noted. He considers it due to toxic products generated by the tumor and reports its incidence as approximately 20 per cent. The presence of fever may for a time obscure the clinical picture, cases of this type having been diagnosed as pyelitis or tuberculosis.

Metastases are common in renal neoplasm and every case of suspected renal tumor should be subjected to a careful ex-

amination clinically and by x-ray. These tumors metastasize through the blood stream and lymphatics. The frequency of pulmonary metastases should be borne in mind. Bony metastases are present in at least 15 per cent of the cases, emphasizing the value of radiographic examination of the long bones and skull.

The metastatic type is of considerable interest from the diagnostic point of view, especially in those cases where pain, hematuria and tumor are absent. We have had at least half a dozen such instances, in which metastatic lesions were the earliest evidence of disease, and the diagnosis of renal neoplasm was established only after a biopsy of the metastatic lesion led to careful study of the urinary tract. In one instance, a woman of fifty-five observed vaginal spotting for five weeks, then had noticed a swelling in the vagina for which she consulted her physician. Examination revealed a mass protruding from the vagina, of which a biopsy was made and reported hypernephroma. Attention was then naturally directed to the kidneys. There was no palpable tumor or pain, and careful examination of the urine revealed a few red blood cells. Cystoscopy and pyelography demonstrated a renal neoplasm. Nephrectomy was performed and the tumor proved to be a hypernephroma.

Varicocele as a symptom associated with renal neoplasm was first described many years ago, and is occasionally encountered. It differs from idiopathic varicocele in that it does not disappear on lying down.

Hypertension has not been found of special diagnostic import, although its association with renal neoplasm has in late years been stressed by numerous observers. Included in the clinical examination is a careful urinalysis. Occasionally, as in two of our cases, the diagnosis was established by finding tumor cells in the urine.

The most important aids in establishing the diagnosis of renal neoplasm are roentgenology combined with cystoscopy, retrograde pyelograms, and in recent years, intravenous urography. Cystoscopy and ureteral catheterization are of

considerable value, of course, in detecting the side involved. In over 90 per cent of the cases cystoscopy demonstrated either blood or impaired function of the diseased kidney. Manipulation of the ureteral catheter in the pelvis of the kidney so as to produce bleeding from the growth is of value when the patient is cystoscoped at a time when the urine is clear. Examination of the catheterized urine for tumor cells occasionally yields positive results.

Roentgenography is an invaluable diagnostic aid, and under this heading four methods are now available.

Simple roentgenography of the kidney frequently gives important information by determining the outline, size, form and position of the kidney. Unilateral increase in size or irregularity of the kidney should be regarded with suspicion. Calcifications in the tumor are occasionally noted and must be differentiated from stone and tuberculosis. The association of stone with renal neoplasm is rather infrequent, although we have noted it at least half a dozen times.

Pneumoroentgenography consists in the introduction of carbon dioxide into the perirenal tissues. We have had very little experience with this method in renal neoplasm but have found it of considerable value in outlining adrenal growths.

Urography of course is the most valuable diagnostic procedure at our disposal, and of the two methods—intravenous and retrograde pyelography, we have found the latter of much more value. In over 80 per cent of our cases there were definite pyelographic changes, indicative of neoplasm. In at least 10 to 15 per cent the interpretation of the pyelogram was exceedingly difficult, either the small size of the tumor produced insignificant pyelographic changes, or the deformities were not sufficiently characteristic to be differentiated from those caused by some of the lesions mentioned below. When in doubt, another pyelogram should be taken a few days later supplemented by intravenous urography. Occasionally, the intravenous dye is reflexly inhibited by the trauma of ureteral catheterization, and there is failure of visualization. It is therefore advisable



as a routine procedure to do intravenous urography before resorting to instrumentation.

Pyelograms of kidney tumors are so varied and bizarre in appearance that it would require too much time and space to describe the many changes encountered. There are any number of varieties of deformity and filling defects of the pelvis, calyces and ureter. In general, the characteristics of renal



Fig. 82.—Carcinoma of kidney. Tumor of upper pole—spreading of calyces

tumor are elongation or obliteration of one or more calyces, filling defects in the pelvis or calyces, displacement of the pelvis or upper ureter and inability of the pyelographic medium to enter the pelvis (Fig. 82). Extrarenal tumors may by pressure or displacement of the kidney produce pyelograms suggestive of renal neoplasm. We have at times encountered considerable difficulty in differentiating enlarged spleens and

retroperitoneal tumors from kidney tumors. A normal pyelogram does not necessarily exclude a neoplasm of the kidney. In three instances in which the tumor was confined to the lower pole of the kidney, without compromising either pelvis or calyces, the pyelograms were perfectly normal.

Intravenous urography has proved itself of considerable value, first by enabling one to obtain a bilateral pyelogram thus aiding in the differentiation between polycystic kidneys and renal neoplasms. It is of course of great help in patients who for some reason or other cannot be cystoscoped. This happened in one of our patients who had so profuse a hematuria that cystoscopy was unsuccessful in determining its source. In infants or children this method often renders cystoscopy unnecessary. The roentgenograms obtained are not as clear in detail as in retrograde pyelography, as good visualization depends on the amount of functioning kidney tissue. Nonvisualization, however, immediately focuses attention to the diseased side and taken in conjunction with other symptoms will often aid in establishing the diagnosis. The differentiation of abdominal masses either intra- or extra-urinary in origin, has been greatly facilitated by this method, so that its use should be a routine one. In general it may be stated that retrograde pyelography gives better detail, and is more reliable in the diagnosis of renal tumor. The main conditions to be considered in the differential diagnosis of renal neoplasm by pyelography are: extrarenal tumors, polycystic kidney, solitary cyst of the kidney, peri- or paranephritis, hydronephrosis, congenital anomalies especially fused kidneys, hypertrophied single kidneys, and filling defects due to uric acid calculus or blood clots in the pelvis of the kidney. Of all the conditions enumerated, blood clots in the pelvis, solitary cyst of the kidney, multilocular cysts not of the true polycystic type, and filling defects due to uric acid stones, give us the most trouble in the differential diagnosis. Colonic roentgenograms aid in determining the retroperitoneal position of the growth in relation to the colon.

The diagnosis of kidney tumors presents but little difficulty

when the classical triad of symptoms is present, or when hematuria and tumor are present. The cases presenting hematuria alone are often difficult to diagnosticate, especially if the functional tests of both kidneys are normal and pyelography is inconclusive. In elderly men where prostatic enlargement is complicated by hematuria, there may occasionally be difficulty in arriving at a diagnosis. One such instance was recently

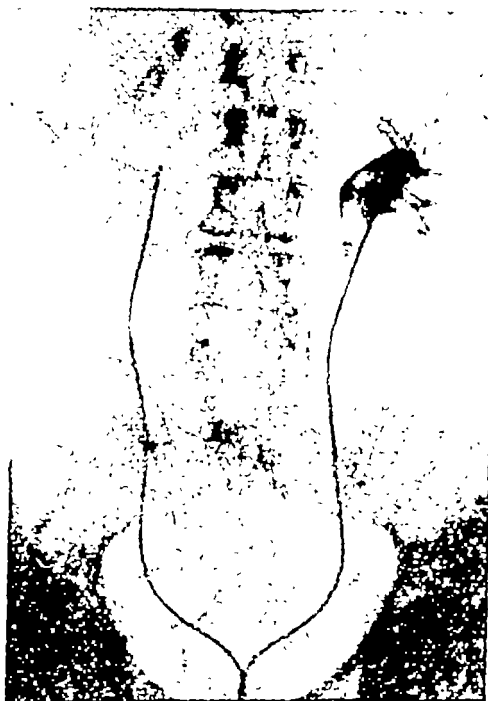


Fig. 83.—Blood clots in pelvis, simulating tumor

seen. The patient, a man of sixty, complained of prostatic symptoms with the appearance of red blood cells in the urine. Flat films of the urinary tract were negative except for prostatic calculi. An observation cystoscopy showed an enlarged prostate and since the function of both kidneys as determined by indigo carmine was normal, the ureters were not catheterized. The red blood cells were thought to come from the enlarged congested prostate. A gross hematuria ensued a few

months later which led to more careful examination of the upper urinary tract by means of ureteral catheterization and pyelography. This demonstrated a tumor in the pelvis of the kidney. Occasionally, despite all our methods of instrumental and radiographic examination, one is left in doubt as to whether or not we are dealing with a renal neoplasm (Fig. 83). Under such circumstances exploratory operation is advisable.

#### TUMORS OF THE KIDNEY IN CHILDREN

Tumors of the kidney in children are practically all of the type known as the Wilms or mixed tumor. These tumors are supposed to take origin in embryonic tissue and are composed



Fig. 84.—Huge Wilms tumor in two-year-old child.

of collections of epithelium in the nature of tubular or glandular structures containing besides smooth and striped muscle fibers, cartilage, bone and proliferating tissue of mesothelial origin.

Clinically, these tumors in children manifest themselves by characteristics distinctly opposite from those seen in adults. The first symptom noticed in many cases is the presence of a large abdominal mass which may reach an enormous size, almost filling the entire peritoneal cavity and producing marked distention of the abdomen. Despite this large tumor, the child may look perfectly well, cachexia not appearing until some time later.

In a certain percentage of cases the disease first manifests itself by anemia, gastro-intestinal symptoms and loss of weight. Pain is not a predominant symptom and if present is not severe. As contrasted with tumors in adults, hematuria is of infrequent occurrence either as an initial symptom or at any stage of the disease. The diagnosis is not difficult. The same urological examinations practiced in adults can usually be carried out in children. Intravenous urography is especially of value, often rendering cystoscopy unnecessary (Fig. 84). Distant metastases are not as common as in tumors in adults, whereas involvement of the retroperitoneal glands occurs frequently.

#### NEOPLASMS OF THE BLADDER

For practical purposes we have found the following classification of bladder tumors meets most requirements. Although fibromata, angiomata, and other rare growths have been described, the great majority of cases presenting themselves for diagnosis belong to the epithelial group.

- (A) 1. Papillomata, benign.  
2. Papillomatosis.
- (B) Papillary carcinoma.
  - (a) Superficial.
  - (b) Infiltrating.
- (C) Nonpapillary infiltrating carcinoma.
  - Adenocarcinoma.
  - Medullary carcinoma.
  - Squamous-cell carcinoma.

The most prominent symptom of bladder tumor is painless hematuria. The character of the bleeding varies according to the location of the growth, as for example, tumors at

the neck may only manifest themselves by terminal hematuria. The bleeding may be only microscopic, or total in character with the passage of clots. In certain cases an initial hematuria may disclose a large growth which evidently has existed for some time. Usually the benign growths produce no vesical irritation unless they are situated at the neck of the bladder. In malignant infiltrating tumors, infection of the urine generally takes place, resulting in dysuria and pain which may become very severe, rapidly undermining the patient's health. With increasing infection the urine becomes alkaline and incrustations form on the growth, adding to the patient's suffering. When the tumor is situated around the ureteral orifices, obstruction of the ureter may ensue, resulting in ureterohydronephrosis. Secondary infection of the kidney may further complicate the picture by causing symptoms of renal insufficiency. Distant metastases, especially osseous involvement, appear late in the course of the disease, although some observers have reported an incidence as high as 30 per cent. In a series of 16 cases of bladder carcinoma that had complete autopsy examinations, we found that 14 showed no evidence of metastases.

In all cases suspected of having a bladder tumor, a careful bimanual rectal or vaginal examination should be made for evidences of infiltration. Since the symptoms enumerated above may be caused by vesical conditions other than neoplasm, a routine urological examination is necessary in order to make a correct diagnosis. The most important diagnostic procedure is of course cystoscopy. The majority of tumors are situated on the base of the bladder, especially in the region of the ureteral orifices. It is usually possible to differentiate cystoscopically between the truly benign papillomata and carcinomata. Edema around the base of the growth and incrustations on the surface generally speak for malignancy. The relation of the tumor to the ureters should be carefully noted. Ureteral catheterization is indicated in every case where the growth is in close proximity to the orifice. At the same time by means of functional tests and pyelography an exact status

can be determined of the upper urinary tract. Biopsy specimens should always be obtained, our experience showing that there is no danger in spreading the disease by this procedure.

There are a number of cystoscopic pictures which may closely simulate bladder tumors. Intensive treatment of a benign papilloma by fulguration may cause a massive edema at the original site of the tumor, simulating an infiltrating malignant growth. A stone impacted at the ureteral orifice, or a



Fig. 85.—Carcinoma of bladder—tumor outlined by umbrathor and air inflation

tuberculosis of the kidney and ureter, may produce massive polypoid edema simulating a neoplasm. Sigmoid diverticulitis, carcinoma of adjacent organs, as rectum, uterus or ovary, may cause changes in the bladder mucosa suggestive of carcinoma of the bladder. Edema of the sphincter region caused by prostatitis, carcinoma of the prostate, and severe cases of cystitis cystica, bilharziasis, and syphilis are other lesions which may simulate a bladder tumor. Biopsy examinations will in

most instances serve to differentiate the various conditions mentioned.

Cystography is another important diagnostic aid. We use 6 per cent iodide supplemented by injections of air (Fig. 85). Such pictures will show changes in the bladder wall caused by infiltration, or the tumor itself may be seen projecting into the bladder. It will also serve to demonstrate tumors growing in a diverticulum by demonstrating a filling defect. Excretory urography is another valuable diagnostic aid, and in addition to the cystogram we obtain accurate information as to the condition of the upper urinary tract.

#### TUMORS OF THE URETER

Primary tumors of the ureter are relatively rare. We are mainly concerned with the epithelial growths, of which there are three varieties—papillomata, papillary carcinoma, and nonpapillary carcinoma. The true papilloma resembles the typical papillomata of the bladder and is generally multiple. The papillary carcinomata have a definite tendency to metastasize and involve regional and retroperitoneal lymph glands. These tumors are more often found in the lower segment of the ureter. The solid nonpapillary carcinomata account for almost 50 per cent of the primary ureteral neoplasms. Up to within a few years ago, 68 cases of primary carcinoma of the ureter have been reported in the literature. An index of the relative occurrence of these tumors, we may cite our series of 209 cases of renal neoplasms recently reported; during the same period of time we observed 5 cases of ureteral carcinoma.

The symptomatology closely simulates that of renal neoplasm, pain, hematuria, and tumor constituting the triad of symptoms generally observed. Although hematuria may occasionally be absent, it is the outstanding symptom and occurs in at least 80 per cent of the cases. The hematuria differs in no wise from that of renal neoplasm. Pain is noted frequently either in the lumbar region dull in character or colicky, due to the passage of blood clots. If the growth invades adjacent structures the pain may simulate a severe sciatica or



lumbago. As a result of ureteral obstruction by the tumor, sooner or later there develops an ascending ureterohydronephrosis and the kidney becomes sufficiently enlarged to present a palpable tumor in the loin. Occasionally the growth may be palpated by vaginal or rectal examination. Small fronds of tumor tissue or atypical cells found in the urine may arouse suspicion as to the nature of the condition. The diagnosis can only be definitely established by careful cystoscopic and radiographic studies. An x-ray examination will generally rule out calculus. We must depend on cystoscopy, ureteral catheterization and urography to definitely establish the diagnosis. Occasionally, as happened in one of our cases, the tumor can be seen projecting from the ureteral orifice. A biopsy specimen was then removed confirming the diagnosis. The ureteral catheter generally encounters an obstruction. This obstruction followed by a copious flow of blood is characteristic of tumor. Obstructions in the ureter may be due to stone, tuberculosis or tumor. The absence of typical scratch marks on a wax bougie will rule out a calculus.

Retrograde urography by demonstrating an irregular filling defect gives valuable information. The filling defect produced by a uric acid calculus is generally more regular in shape, whereas that due to tumor has a moth-eaten appearance. Pyelography and intravenous urography will give us information as to the condition of the kidney and the ureter above the site of the obstructing neoplasm. Some of these cases show quite an advanced hydronephrosis, and many patients have been operated on for this condition, subsequently to be reoperated for the removal of the lower ureter with its tumor. Metastases are rather common, involving mainly the retroperitoneal nodes, liver and lung. Naturally all cases should have radiography of the chest before operative interference is considered.

#### CARCINOMA OF THE PROSTATE

Malignant disease of the prostate occurs in approximately 15 to 20 per cent of all patients with prostatic disease. The

local symptoms closely simulate those of benign prostatic obstruction. Gross hematuria is less typical of malignancy than of the benign type. Rather characteristic of malignancy are radiating pains in the back or thighs, often attributed to sciatica or lumbago. The diagnosis of malignancy rests on prostatic palpation. At least 80 to 90 per cent of prostatic cancers can be detected by rectal palpation. The characteristic signs are induration, fixation and nodulation. The gland may be large or small, only one nodule may be palpated or the entire gland may be riddled with nodules. Since osseous metastases are commonly seen, radiograms of the bones, especially the pelvis and spine should be routinely carried out. There are borderline cases of the chronic inflammatory type which closely simulate a malignant gland in its hardness. Prostatic calculi have been diagnosed as prostatic carcinoma; another reason for an x-ray examination to exclude this error. Cystoscopy, of course, should always be done. Distortions of the internal sphincter orifice, associated with edema are often deciding factors in establishing the diagnosis. When in doubt an aspiration biopsy of the gland through the perineum will often give us valuable information. In a recent case in which the diagnosis could not be definitely established by rectal palpation, cystoscopy disclosed a slight edema of the mucosa overlying the internal sphincter. By means of the resectoscope a few segments were resected from this region, and a definite diagnosis of carcinoma was made by histological examination.

#### MALIGNANT DISEASE OF THE TESTICLE

Every scrotal swelling should be carefully examined for the possibility of an underlying neoplasm. What appears to be a simple hydrocele may, after tapping, reveal an enlarged testicle which may prove to be a teratoma. Despite the fact that the testicle is an exposed organ easily palpated, the differential diagnosis of the underlying condition is not so simple. Teratomas at times develop so rapidly that when the patient is first examined metastases may already be present. The patient should be examined both in the erect and reclining positions.

Testicular tumors are generally unilateral, and occur more frequently in young people. The tumor is usually smooth and elastic although some neoplasms have areas cartilaginous in consistency. The growth is almost always limited to the testicle, the epididymis feeling normal. The testicle is usually insensitive, the overlying skin looks normal unless the growth is very large, then the skin has a glazed appearance. The spermatic cord is normal and generally sharply demarcated from the tumor. Often there is an inflammatory hydrocele which yields clear fluid on tapping. A bloody tap generally denotes invasion of the epididymis. On standing, the testicle has a feeling of weight to it. Inguinal or femoral lymph nodes are not involved until late in the course of the disease. Intra-abdominal and retroperitoneal metastases are rather common, so a careful abdominal examination should always be made. Roentgenograms of the chest should be taken routinely for the presence of metastases. Incision into the tumor for biopsy should never be undertaken, as the tumor is likely to spread rapidly and fungate following this procedure. Instead, an aspiration biopsy with a small needle is preferable. The use of the Aschheim-Zondek test as a diagnostic procedure should always be resorted to, although the limitations should always be borne in mind. Dean has recently summarized the results of this test as follows, "Assuming the patient appearing for examination with an enlarged testes of three months' duration, that he has received no treatment, and that there is no evidence of metastases.

"1. If the test is negative it is probable that he has no teratoma. It is possible that he has an adult teratoma which has not destroyed the interstitial cells of the testes.

"2. If the test shows 500 or less mouse units per liter of urine it is probable that the patient has a teratoma. This may be of an adult type, such as an adult cystic teratoma that has largely or wholly destroyed the interstitial cells of the testis, or it may be a smaller tumor of a low grade of malignancy which has not destroyed the interstitial cells. It is possible that the testis is the seat of syphilis, tuberculosis, interstitial

orchitis or any other condition that would cause swelling and complete destruction of the interstitial cells. It should be understood that it is exceptional for a testicle affected with syphilis, tuberculosis or interstitial orchitis to have all the function of the interstitial cells destroyed so that a positive test is obtained.

"3. If the test shows between 500 and 1000 mouse units per liter of urine, the tumor is probably a seminoma.

"4. An output of between 2000 and 10,000 mouse units per liter indicates an embryonal carcinoma with lymphoid stroma.

"5. An output of more than 10,000 mouse units per liter of urine indicates an embryonal adenocarcinoma or a chorio-epithelioma."

If a man has an untreated tumor of the testis and evidence of metastases, the Aschheim-Zondek test will be positive with probably more than 1000 mouse units per liter output.

As regards the differential diagnosis, the conditions simulating testicular neoplasm are tuberculosis, gumma, hematoma, and torsion of the spermatic cord.

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VOL. 20—65



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### COMMON UROLOGIC CONDITIONS IN CHILDREN

ABOUT half of all children suffer some form of urologic disturbance before reaching puberty. In a large portion of these children, the disturbance is minor and frequently passes unrecognized. In the others the uropathy is of major importance and is sometimes fatal. In the majority of children with important urologic lesions, correct early interpretation of the presenting symptoms and a careful urinalysis will at once direct attention to the urinary tract.

A plea is herewith made for a careful examination of the urine in *any* sick child. Moreover, urinalysis should be performed in all children subjected to routine physical examination. In an astounding number of young patients in whom I have performed complete urologic examination, the discovery of an asymptomatic persistent pyuria occurred at the time of a routine urinalysis, when urologic disease was not even suspected.

Urologic conditions in children are here grouped according to the dominant symptom. It might be more fitting to entitle the communication Usual Causes of Common Urologic Symptoms in Infants and Children. Pyuria, disturbances of urination or nephritis are most commonly observed. The pyuric group are usually said to have either acute or chronic pyelitis. The clinical picture in the group showing disturbances of urination is usually called enuresis. Nonsuppurative nephritis

—Bright's disease—may be omitted from the present discussion. Other somewhat less frequent presenting manifestations are hematuria and pain or tumor along the urinary tract. These five symptoms constitute the principal indications for urologic examination in the young and the common lesions which may cause them are herewith briefly discussed.

### PYURIA

Pyuria is the usual manifestation of urinary infection and always exists in the latter except during the first twenty-four hours of the disease in rare instances of hyperacute renal infection. Acute pyelonephritis, commonly designated as acute pyelitis, is usually correctly diagnosed, and with relatively simple therapeutic attentions generally runs a self-limited course. Although most of these patients are symptomatically cured within two weeks and the urinalysis is commonly negative after a month, in a large portion culture of the urine as late as six months after the acute illness, will show persistence of the etiologic organisms. In these cases of persistent bacteriuria, recurrences of acute renal infection are clinically recognized as recurrent acute pyelitis and are likely to appear with each acute focal infection elsewhere (tonsillitis, enteritis, etc.) or with the onset of acute urinary obstruction. In some children with acute renal infection a pyuria will persist after the patient becomes symptomatically well. If this pyuria resists intensive medical therapy for two to four weeks a complete urologic examination is indicated. In most of these cases a urinary anomaly which causes either obstruction or stasis will be found. In short, chronic pyuria and anomalous development of the urinary tract in children, are almost reciprocal.

Before subjecting the child to a complete urologic examination because of persistent pyuria, an *intensive course of medical treatment* is indicated. This includes urinary antisepsis which must be administered in much larger doses than customarily employed. My preference is methenamine (urotropin) and the basis of dosage is 10 to 12½ grains per day

per year of age. Thus a five-year-old child receives 50 to 65 grains in twenty-four hours. In children I have given twice this amount without untoward effect. As Helmholtz has shown, the therapeutic coefficient of methenamine is directly proportional to the urinary acidity. In methenamine therapy one should attempt to get the urine as near pH 5.5 as possible. At this titer methyl orange paper turns red and this indicator should be used rather than litmus paper. This acidulation can best be achieved by the use of ammonium chloride (which I prefer), ammonium nitrate or calcium chloride. These chemicals are available in enteric coated pills. The dose of acidulant usually equals that of the methenamine but must necessarily be altered to achieve or maintain the desired high acidity (pH 5.5). Recently I gave a young boy 200 grains of ammonium chloride before the desired acidity existed but once achieved, it was continued with less than half this dose. The medication is intensively given for four or five days when a rest period of a day or two is observed and during which time the urine is carefully examined, including culture. If infection remains the medication is resumed for another four days. As a rule, it is useless to persist with antiseptics longer than two weeks for if the urine cannot be sterilized in this time by this method, further similar efforts are likely to be futile. In infants the medication is given in the formula. With older children it may be given in solution with a palatable syrup. Hematuria induced by formaldehyde cystitis (urotropin reaction) is purely of vesical origin and will promptly disappear with withdrawal of the medication. Yet the vesical reaction is a favorable rather than unfavorable manifestation; it indicates an appreciable concentration of formaldehyde in the bladder urine.

Other urinary antiseptics include caprokol, pyridium, serenium, neutral acriflavine and methylene blue but if methenamine therapy is unsuccessful these other antiseptics are almost certain to fail.

The *kctogenic diet* is successful in sterilizing the urine of children in about 60 per cent of the cases. I have frequently



employed it following surgical treatment. It should be pointed out here, however, that the ketogenic diet will often sterilize the urine in patients with important anomalies of the urinary tract and for this reason a urologic examination is indicated in these patients even though, during the therapeutic period, the ketogenic diet was successful. In other words, the previous persistence of the urinary infection at once suggests the likelihood of a urinary anomaly and obstruction.

*A correct anatomic diagnosis in chronic pyuria can be made only by a complete urologic examination.* Residual urine may be present or the x-ray may demonstrate a urinary calculus. Although intravenous urography will often suffice to establish the diagnosis, in most instances it should be considered only a precystoscopic measure with which to elicit as much information as possible before the instrumentation is attempted. A complete urologic examination including cystoscopy, ureteral catheterization, divided renal function tests and retrograde pyelography can be performed without general anesthesia in about three fourths of all children. During the past four years in boys of three years and over I have used caudal anesthesia more than one hundred and fifty times. During the past year and a half I have used intravenous anesthesia (evipal) for brief instrumentation in more than 100 cases. It is fitting to note here that instrumental reactions following complete urologic examination in children are less than half as frequent and severe as in adults. Fear of an unfortuitous reaction need never be considered a contraindication to cystoscopic examination in a child.

*Obstruction* is the principal predisposing cause of urinary infection. The urinary tract above the obstruction becomes congested. The congested organ is more vulnerable to bacterial attack than the normal organ and organisms which are continually reaching the kidney by the blood stream find a suitable soil for growth. Not only does obstruction predispose to infection but once infection is established in the presence of obstruction the former can rarely be eliminated until the blockage is eradicated. Neuromuscular inertia such as is commonly

observed in cord bladder disease must also be considered as a cause of urinary stasis.

The common potential causes of urinary obstruction and by the same token the common predisposing causes of urinary infection are shown in Fig. 86. There may be a congenital stenosis of the preputial orifice or a stricture of a renal calyx. Between these anatomic extremes one or more of a legion of uro-obstructive conditions may exist. I have seen several boys said to have chronic pyelitis, but in whom the pyuria was proved to be perpetuated by a tight prepuce. Circumcision or a generous dorsal slit was commonly followed by a disappearance of the pyuria. This justifies the conclusion that the pyuria resulted from subpreputial urinary retention, stagnation and infection. Frequently the meatus is congenitally tight and produces urinary stasis. I have encountered this many times in boys and in a few girls, in some of whom the urinary back-pressure caused dilatation of the entire upper urinary tract. In a girl of thirteen months with congenital stricture of the anterior urethra, the cystographic bladder picture resembled that observed in advanced prostatic obstruction. Lesions commonly found in the deep male urethra are congenital valves, hypertrophy of the verumontanum, and congenital contracture of the vesical outlet. All of these may cause urinary obstruction with severe back-pressure; renal damage and important infection must eventually be anticipated. The majority of cases of these types that I have studied clinically were examined because of persistent pyuria.

*Neuromuscular disease*, usually designated as cord bladder, is not uncommon in children. There are 79 cases in my series. It is frequently associated with anomalies of lower spinal or neural development. Marked spina bifida occulta is frequently found in these cases. On the other hand, in some of the most advanced instances of cord bladder in children and with residual urine as much as 16 ounces, careful neurologic examination of the lumbosacral innervation failed to reveal alterations in either sensation or motor control. Occasionally in these

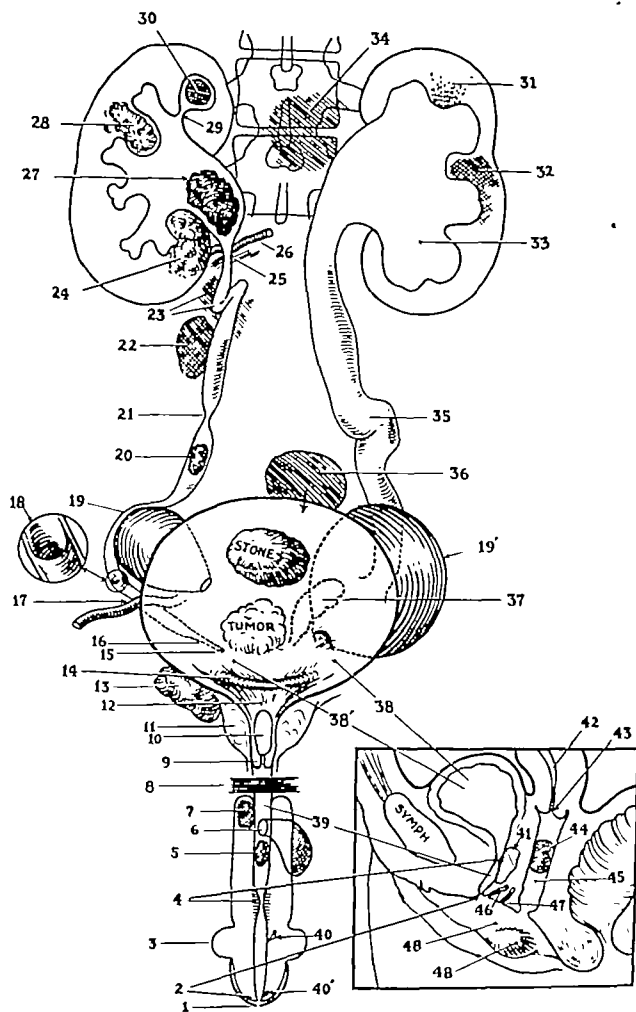


Fig. 86.—Direct and indirect causes of pyuria in children. 1, Stenosis of prepuce; 2, stenosis of meatus; 3, paraphimosis; 4, urethral stricture; 5, urethral stone; 6, urethral diverticulum; 7, periurethritis, periurethral abscess; 8, cowperitis; 9, congenital valves of posterior urethra; 10, hypertrophy of verumontanum; verumontanitis; 11, prostatitis; prostatic abscess; 12, contracted bladder neck; median bar; 13, periprostatis or abscess; 14, mucosal fold at bladder outlet; trigonal curtain; 15, stricture of ureteral meatus, ureterocele; 16, ureterovesical junction stricture; 17, aberrant vessel; 18, congenital ureteral valves; 19, ureteral obstruction by diverticulum compression; 19', diverticulum, ureter opening into diverticulum; 20, ureteral stone; 21, ureteral stricture; 22, periureteritis; periureteral phlegmon or abscess; 23, ureteral kink; periureteral fibrous bands; 24, renal tumor; 25, ureteropelvic junction stricture; 26, aberrant vessel obstruction of upper ureter; 27, pelvic stone; 28, renal tuberculosis;

cases laminectomy is of value but generally the prognosis is unfavorable.

*Bladder stone* and diverticula are commonly associated with pyuria and are secondary complications in about 5 per cent of all cases of infravesical obstruction.

*Congenital stricture of the ureter* is the commonest obstructing lesion of the upper urinary tract. Except in the presence of infection congenital ureteral strictures rarely show sclerosis; they are merely anomalous narrowings comparable to similar narrowings frequently seen in the esophagus, at the pylorus, further down in the intestinal tract, and in the larger biliary ducts. Ureteral strictures occur most often at the lower end of the tube, are next most common at the upper end and are rarest in the middle. Frequently they are bilateral and may be multiple but I have never seen more than three strictures in one ureter. In 12,080 pediatric autopsies which I have recently tabulated, congenital ureteral stricture occurred in 72 instances (1:168). Yet it is an extremely common clinical finding in children with chronic pyuria (101 of 580 cases or 17.3 per cent). The demonstration of stricture requires a careful urologic examination. Many congenital strictures can be adequately treated by ureteral dilatation; for this purpose I have recently devised a special miniature dilating cystoscope (No. 17 F.) which will take a bougie as large as a slate pencil (No. 10 F.). This permits ample ureteral dilatation for any child up to the age of puberty.

It is axiomatic that an anomalous organ is more prone to disease than a normal one. Nowhere is this better exemplified than in ureteral reduplication, a condition found in about 0.5 per cent of all individuals. In 26,480 autopsies we found 136 cases reported, an incidence of 1:195. Yet in 580 children

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29, stricture of caliceal outlet; 30, caliceal stone; 31, pyelonephritis; 32, pyonephrosis; 33, hydronephrosis; 34, perirenal suppuration; spinal disease (Potts', etc.), 35, hydroureter; 36, pericystic abscess rupturing into bladder; 37, seminal vesiculitis; 38, neuromuscular vesical disease; 38', cystitis; 39, urethritis; 40, folliculitis (Littre'); 40', folliculitis (Morgagni); 41, periurethritis; periurethral abscess; 42, endometritis; 43, cervicitis; 44, foreign body in vagina; 45, vaginitis; 46, skenitis; 47, folliculitis of introitus; 48, Bartholinitis; Bartholin abscess.

with persistent pyuria there were 58 cases (1:10) of ureteral reduplication, nearly twenty times the normal incidence. In all of these children the anomaly was a fundamental factor in causing the pyuria to persist. In many of these cases both divisions of the ureter and of the reduplicated kidney were involved by infection or obstruction. Yet in a surprising number only half of the reduplicated organ was diseased and in 13 children ranging in age from five months to eight years ureteroheminephrectomy (removal of the diseased half of the kidney and the reduplicated ureteral segment draining it) cured the pyuria.

In some instances the ureteral orifice is ectopic and opens in the urethra or, rarely, in the vestibule. A ureter with an ectopic orifice almost always shows evidence of urinary stasis, and infection is an extremely common complication. In a girl of thirteen months with persistent pyuria since the age of five months urologic examination revealed complete bilateral ureteral reduplication. The ureter from the lower pelvis of the kidney on each side opened normally in the bladder. The ureter from the right upper pelvis—and this was uninfected—opened in the posterior urethra. The ureter from the pyonephrotic upper segment of the left kidney opened in the vestibule. By squeezing the left loin thick pus resembling toothpaste was seen to exude from the ectopic opening in the vestibule. Ureteroheminephrectomy cured.

*Ureteral calculi* are occasionally found. In a girl of nineteen months examined because of chronic pyuria, a small uric-acid stone was seen in the bladder and two uric-acid stones were demonstrated by negative pyelography and scratch of a wax bulb in the left ureter, on which side the pyuria originated. Spontaneous passage of these stones followed instrumental dilatation of the ureter.

*Aberrant vessels* are frequent causes of ureteral obstruction. About a fourth of all kidneys show anomalous vessels which pass from the upper pole or from the lower pole, chiefly to the vena cava or aorta. Those vessels which pass from the lower pole cross, and frequently cause pressure on the upper

ureter. This induces hydronephrosis which often becomes infected and pyuria persists. Quite uniformly these children are said to have chronic pyelitis. I have now operated on 17 cases of vascular obstruction of the ureter in children. In three of these, antecedent attacks of Dietl's crises induced by the vascular obstruction had caused the appendix to be removed. When renal injury is not marked, resection of the vessels is frequently curative. Most children, however, are not seen until the hydronephrotic damage is extreme and nephrectomy is required.

Rarely, an anomalous vascularization in the depths of the female pelvis may cause ureteral obstruction. The uterine artery is usually the obstructing vessel but a branch of the iliac or hypogastric vessels may cause the pressure. In a child of thirteen months with persistent pyuria the diagnosis of vascular obstruction of the lower ureter was made by urography and was confirmed at operation. An artery, vein and band of fibrous tissue firmly compressed the ureter at a point 1 cm. above the ureterovesical junction and was indicated in the urogram as a transverse filling defect. I have seen apparently this same condition in three other young children but in whom the diagnosis lacks surgical confirmation.

*Stones in the kidney* are not uncommon in children; there are 10 cases in my personal series. I have removed a kidney for stone pyonephrosis from a boy of six months and from a girl of two years. Doubtless most of the small renal stones of childhood pass spontaneously; the painful syndrome accompanying their passage is usually interpreted as intestinal colic. Many calculi in childhood are composed of pure uric acid and hence are not radiopaque. They must be demonstrated either as (1) negative or vacuolated shadows in the radiographic media or (2) by passage of a wax-bulb ureteral bougie which the stone scratches. Sometimes renal stones in children can be removed by simple pyelotomy.

*Chronic suppurative pyelonephritis* is occasionally found. In some of these cases neither antecedent obstruction nor any other predisposing factor can be demonstrated at the time the

examination is made. Moreover, identification of these etiologic factors is frequently obscured by marked secondary inflammatory changes in the ureters and renal pelves.

*Chronic renal tuberculosis* must not be overlooked. One in every 50 cases of so-called "chronic pyelitis" in children is surgical renal tuberculosis. The dominant clinical manifestations almost always lead to the diagnosis cystitis—acute or subacute. Having established the diagnosis nephrectomy, when not contraindicated by bilateral renal involvement or by functional insufficiency of the "better" kidney, offers the only hope of cure. There are 18 cases in my series.

#### DISTURBANCES OF URINATION

Dysuria or difficulty in urination is most often due to congenital obstruction in the prostatic urethra but vesicosphincterospasm caused by inflammation may produce this symptom in both males and females. Moreover, I have seen several cases of extreme dysuria in young boys with a congenitally tight meatus; in many of these cases secondary ulceration—the ulcerated meatus—occurred. Meatotomy cures the meatal obstruction; transurethral resection of the deep congenital urethral obstructing lesions is the usual indicated treatment.

*Enuresis* is the commonest disturbance of urination in children and doubtless in 95 per cent of the cases is purely a functional disorder. We strongly believe, however, that urologic examination is indicated in those enuretic children uncured in two to three months by medical, physical or psychologic therapy. In a personal series of 532 children thus subjected to cystoscopic examination, uropathy adequate to explain the clinical picture was found in 60 per cent. Fifteen per cent of the latter children had residual urine, that is, they could not empty their bladders. In females with enuresis urethrotigonitis is the commonest lesion found. In enuretic males congenital obstructive lesions at the bladder neck or in the posterior urethra are of high incidence. In children of all ages inflammation due to unsuspected urinary infection is often the fundamental etiology of the enuresis and in 3 instances

in my series nephrectomy for renal tuberculosis was the essential treatment. Although one wishes to believe that well-trained pediatricians would not fail to recognize enuretic manifestations due to a tight prepuce or meatus, bladder stone, chronic pyelonephritis or renal tuberculosis, for example, my

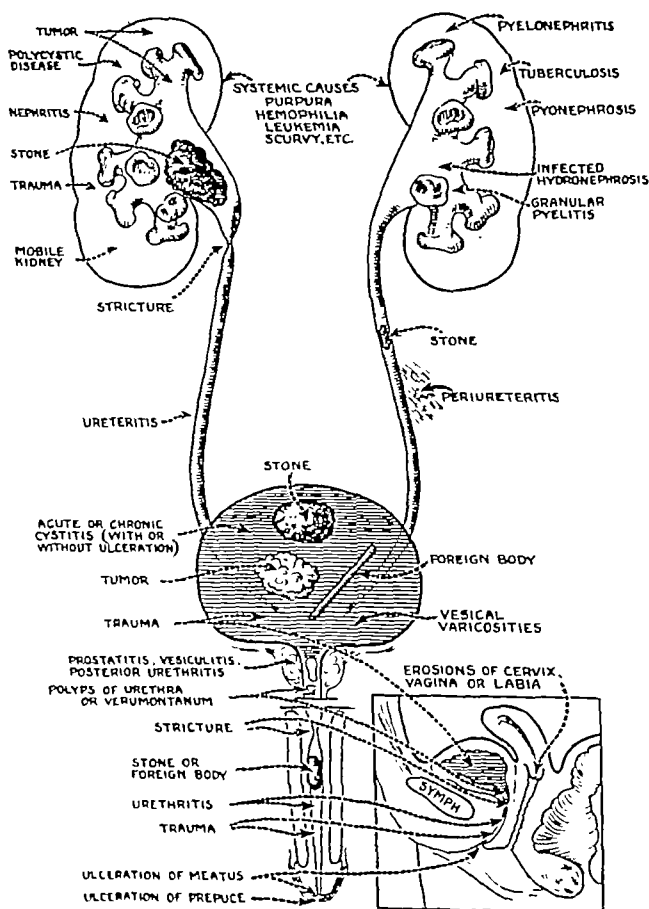


Fig. 87.—Usual sources of hematuria.

experience has shown that this unusual conception of the potential etiology of so-called "enuresis" is not generally held.

When no urologic basis for the enuresis is found psychotherapy may be continued with the assurance that no important disease is progressing in the urinary tract. When a urologic



lesion is demonstrated, the treatment is based entirely on pathology. In a great many girls with urethrotrigonitis, ample dilatation of the urethra and the local use of dilute silver nitrate is curative—the identical treatment commonly employed in urethrotrigonitis in adult women.

### HEMATURIA

Hematuria in a child usually means nephritis, renal tumor, or renal tuberculosis. Yet in several boys with moderately profuse hematuria the bleeding came from an ulcerated meatus. Except when due to acute glomerular nephritis hematuria always indicates a thorough examination. Occasionally the bleeding results from renal congestion coincident to an obstructive lesion. The commonest causes of hematuria are shown in Fig. 87.

### PAIN

Pain is seldom the only symptom of urologic disease in children. The most striking instance I have observed occurred in a five-year-old girl with a congenital ureteral kink. Her only complaint was pain in the left renal region; urinalysis was thoroughly normal. Urologic examination revealed a fixed kink at the junction of the middle and upper third of the left ureter and with the mobilization of the kink and high fixation of the kidney, the pain disappeared. Periodic ureteral dilatation now insures free drainage.

### TUMOR

*Embryonal adenomyosarcoma of the kidney* is the commonest abdominal tumor of children, and of all tumors in children is outranked only by those of the orbit. These renal tumors (Wilms) are commonest before the age of five years; are seldom correctly recognized until the growth is far advanced, and to date the mortality has been about 95 per cent. Of 52 cases, only 2 lived five years. I have 3 cases which appear to be cured more than one year postoperative. One of these is a girl from whom an embryonal adenosarcoma weighing 500 Gm. was removed at the age of six weeks; she shows

no evidence of recurrence one and one-half years later. In cases of this highly malignant tumor recurrences are usually noted within six months and patients who show no recurrence within a year will probably remain cured. Nephrectomy offers the only hope of cure and the combined use of irradiation therapy and nephrectomy offers the only prospect for reduction of the present mortality. Preoperative irradiation totaling 3000 to 5000 r. should be given in divided daily doses over a period of about three weeks (Coutard technic). As a result of this irradiation many of these renal tumors will become no longer palpable. Three to four weeks following the irradiation the kidney should be removed. A month postoperative a course of irradiation similar to the preoperative therapy should be given. Because metastasis is frequent, the irradiation should include the abdomen and chest although not so intensively as the primary tumor.

*Neuroblastoma of the adrenal* simulates and is usually erroneously diagnosed renal tumor. It occurs half as often as renal tumors. Most retroperitoneal "lymphosarcomas" in children are adrenal neuroblastomas. The tumor seldom invades the kidney, it metastasizes widely, and is almost always fatal.

Fortunately not all palpable tumors of the renal region are malignant. *Hydronephrosis* is the commonest palpable renal tumor in children and most commonly results from: (1) congenital stricture at the ureteropelvic junction or (2) vascular obstruction by anomalous lower polar vessels which compress the ureter at or near its union with the pelvis. Preoperatively, the likely etiology of the hydronephrosis can usually be deduced by excretory urography. This diagnostic aid, however, is of no value when the renal function is extremely low; retrograde urography must be employed. In some of these cases conservative surgical treatment, *c. g.*, resection of obstructing vessels or a ureteropelvioplasty will relieve the obstruction. Yet in most children extreme renal damage demands nephrectomy.

*Undescended testicle* is the commonest disturbing condition

of the spermatic tract in boys. Boys with undescended testicle should be given the benefit of hormone therapy (antuitrin-S; follutein). If this fails, the testicle should be brought down into the scrotum, preferably by the Torek procedure and preferably by the eighth year. In cryptorchid patients with a complicating hernia, only surgical treatment merits consideration. It should be noted that in some patients in whom the use of glandular extracts is apparently followed by descent of the testicle, the gland recedes to its former position when the hormone therapy is discontinued.

#### SUMMARY

Attention has been directed to the more common lesions which help to cause chronic pyuria in children. The high incidence of these conditions and the relative infrequency of their correct recognition, especially when the upper urinary tract is involved, is a challenge to pediatricians and urologists alike. In chronic pyuria a congenital anomaly of the urinary tract should be assumed to exist until proved otherwise.

Although enuresis is almost always a functional condition urologic examination of the treatment-resistant cases shows demonstrable pathology in nearly two thirds.

Infants and children tolerate complete urologic examination better than their elders; reactions are only half as frequent and are much less severe in the young patients. Certainly fear of undesirable sequelae should never be permitted to rule against a thorough urologic investigation when it is otherwise indicated.

One admonition more than any other I would give: examine the urine.

## INDEX TO VOLUME 20

- ABDOMINAL diseases causing fever in children, *July*, 21  
     examination in secondary gastro-intestinal tuberculosis, *Nov.*, 857  
     pain in pulmonary tuberculosis, *Nov.*, 854  
 Aberrant vessels, ureteral obstruction due to, *Nov.*, 1034  
 Abortion, diagnostic mistakes, *July*, 76  
     habitual, *July*, 81, 93  
 Abscess, abdominal, in children, *July*, 26  
     mediastinal, in children, *July*, 18  
     of brain in children, *July*, 43  
     of breast, acute, *Sept.*, 627  
     chronic, *Sept.*, 630  
     of kidney, multiple, in children, *July*, 33  
     of lung, multiple, in children, *July*, 18  
         pulmonary bleeding in, *Sept.*, 486  
         perinephric, in children, *July*, 33  
         retropharyngeal, in children, *July*, 13  
         subphrenic, in children, *July*, 26  
 Acidosis in diabetes complicated by tuberculosis, *Nov.*, 836  
 Acinuous nodose tuberculosis, *Nov.*, 706  
 Acne vulgaris, etiology, *Nov.*, 985  
     hormonal treatment, *Nov.*, 985, 990  
 Acnitis, *Nov.*, 1003  
 Acromegaly, *Sept.*, 387  
 Addison's disease, borderline cases, *Sept.*, 345  
 Adenoids, infected, fever due to, *July*, 10  
 Adenomyosarcoma, embryonal, of kidney, *Nov.*, 1038  
 Adiposis dolorosa, *Sept.*, 374  
 Adiposity, cerebral, *Sept.*, 374  
 Adiposogenital dystrophy, *Sept.*, 374  
 Adrenal cortical tumors, *Sept.*, 349  
     insufficiency, borderline cases, *Sept.*, 345  
     neuroblastoma, *Nov.*, 1039  
 Allergic asthma, treatment, *Sept.*, 591  
     infants, colic in, *Sept.*, 512  
 Alternation of heart, *July*, 188; *Sept.*, 545  
 Amebic dysentery in children, *July*, 24  
 Anal obstruction in newborn, *Sept.*, 622  
 Anatomic tubercle, *Nov.*, 1002  
 Anemia and hypothyroidism, *Sept.*, 340  
     nutritional, in infancy, diet in, *Nov.*, 943  
     hemoglobin determination, *Nov.*, 934  
     iron preparations for, *Nov.*, 937  
     management, *Nov.*, 933  
     sickle cell, *July*, 55  
 Angiolupoid, *Nov.*, 1004  
 Antiseptics, urinary, for children, *Nov.*, 1028  
 Appendicitis, acute, in aged, *July*, 133  
     in children, fever in, *July*, 25  
 Appetite in pulmonary tuberculosis, *Nov.*, 853  
 Arcus senilis, *July*, 128  
 Arrhythmias, diagnosis and treatment, *July*, 175  
     significance of, *Sept.*, 537  
 Arsenic encephalitis, *Sept.*, 417  
 Arteriosclerosis in cardiovascular-renal disease, *July*, 209  
 Arthritis, gonorrheal, in male, *July*, 152  
 Aschheim-Zondek test in malignant disease of testicle, *Nov.*, 1024  
 Asphyxia neonatorum, *July*, 99  
 Aspiration in pleurisy, *July*, 329  
 Associated movements, automatic, abnormal, *July*, 227  
 Asthenia, neurocirculatory, simulating hyperthyroidism, *Sept.*, 343  
 Asthma, bronchial, intratracheal injection of iodized oil, analysis of 1000 cases, *Nov.*, 907  
     instrumentarium, *Nov.*, 916  
     reaction following, *Nov.*, 923  
     technical points, *Nov.*, 915  
     other respiratory pathology accompanying, *Nov.*, 926  
     treatment, *Sept.*, 591  
     emphysema in, *Sept.*, 443

- Atelectasis, pulmonary, in newborn, *July*, 106, 111  
 Ateliosis, *Sept.*, 362  
 Atopy, *Sept.*, 652  
 Auricular fibrillation, *July*, 181; *Sept.*, 541  
     flutter, *July*, 184; *Sept.*, 541  
 Auriculoventricular block, *Sept.*, 544  
 Australian X disease, *Sept.*, 424  
 Autohemotherapy in herpes zoster, *July*, 245  
 Autonomic imbalance in newborn, *Sept.*, 623
- BASOPHILISM, pituitary, *Sept.*, 349, 387  
 Beet pulp, laxative value, *Sept.*, 457  
 Birth trauma, vomiting due to, *Sept.*, 623  
 Bladder, cord, in children, *Nov.*, 1031  
     malignant disease, diagnosis, *Nov.*, 1018  
     stone in, in children, *Nov.*, 1033  
 Blepharospasm in parkinsonism, *July*, 228  
 Blood, disorders, genetic aspects, *July*, 253  
     pulmonary bleeding in, *Sept.*, 490  
     iodine, in hyperthyroidism, *July*, 286  
     sugar in diabetes complicated by tuberculosis, *Nov.*, 834  
     vessels, diseases of, pulmonary bleeding in, *Sept.*, 489  
 Bones, diseases, in aged, *July*, 138  
 Botulism, *July*, 265  
     in children, *July*, 28  
 Bowels in pulmonary tuberculosis, *Nov.*, 855  
 Brain abscess in children, *July*, 43  
     tumors in children, *July*, 47  
 Bran in constipation, *Nov.*, 899  
 Breast, diseases of, differential diagnosis, *Sept.*, 625  
 Brill's disease, *July*, 52  
 Bronchi, diseases of, causing bleeding, *Sept.*, 485  
 Bronchial asthma, intratracheal injection of iodized oil, analysis of 1000 cases, *Nov.*, 907  
     other respiratory pathology accompanying, *Nov.*, 926  
     treatment, *Sept.*, 591  
     fistula in tuberculous empyema, *Nov.*, 843, 845  
 Bronchiectasis as cause of fever in children, *July*, 18  
     cough in production of, *Nov.*, 867  
     pulmonary bleeding in, *Sept.*, 485
- Bronchitis, chronic, emphysema in, *Sept.*, 443  
     in aged, *July*, 135  
 Broncholithiasis, pulmonary bleeding in, *Sept.*, 486  
 Bronchopulmonary bleeding, diagnosis and treatment, *Sept.*, 483  
 Bronchoscopy in pulmonary hemorrhage, *Sept.*, 492  
 Brucella melitensis, *July*, 51  
 Bulk-producing drugs in constipation, *Nov.*, 900  
 Bulky foods, laxative value, *Sept.*, 449
- CALCULUS, bladder, in children, *Nov.*, 1033  
     renal, in children, *Nov.*, 1035  
     ureteral, in children, *Nov.*, 1034  
 Carbuncle of kidney in children, *July*, 33  
 Carcinoma of bladder, diagnosis, *Nov.*, 1018  
     of breast, *Sept.*, 641, 642  
     of cervix, diagnostic mistakes in, *July*, 78  
     of kidney, diagnosis, *Nov.*, 1010  
     of lung, pulmonary bleeding in, *Sept.*, 487  
     of prostate, diagnosis, *Nov.*, 1022  
     of testicle, diagnosis, *Nov.*, 1023  
     of ureter, *Nov.*, 1021  
 Cardiac. See *Heart*.  
 Cardiovascular disease in aged, *July*, 139  
     physical exercise in, *July*, 191  
 Cardiovascular-renal disease, preventive aspects, *July*, 209  
 Caseous pneumonia, tuberculous, *Nov.*, 709, 744  
 Cellulose in foods, *Sept.*, 450  
 Cereals, thick, feeding of, in gastroenterospasm, *Sept.*, 518, 519  
 Cerebral adiposity, *Sept.*, 374  
     edema and hemorrhage in newborn, *July*, 105, 109  
 Cervical lymphadenitis in children, *July*, 14  
 Cervix, carcinoma of, diagnostic mistakes, *July*, 78  
 Chancre, tuberculous, *Nov.*, 1002  
 Chickenpox, encephalitis in, *Sept.*, 433  
 Chlorotic marasmus, *Nov.*, 982  
 Cholecystitis, acute, diagnosis, *Sept.*, 472  
     chronic, diagnosis, *Sept.*, 473  
 Cholecystography, intravenous, *Sept.*, 475  
     oral, *Sept.*, 478  
 Cholesterosis, *Sept.*, 473  
 Cogwheel motor rigidity, *July*, 232

# INDEX TO VOLUME 20

- Colds, common, as cause of fever in children, *July*, 9
- Colic, infantile, classification and treatment, *Sept.*, 511
- Colitis, ulcerative, in children, *July*, 24
- Collapse therapy in tuberculosis, *Nov.*, 775
- fluoroscopy and x-ray in, *Nov.*, 819
- Constipation and hypothyroidism, *Sept.*, 340
- bulky foods in, *Sept.*, 449
- chronic, *Nov.*, 891
- treatment, *Nov.*, 894
- in pulmonary tuberculosis, *Nov.*, 855
- rectal, *Nov.*, 895
- Contact dermatitis, *Sept.*, 651, 653
- Contractions of heart, premature, *July*, 177
- Convulsions, uremic, treatment, *Sept.*, 532
- Copper as adjuvant to iron in nutritional anemia, *Nov.*, 941, 948
- Cord bladder in children, *Nov.*, 1031
- Corpus spongiosum, marked induration, in gonorrhea, *July*, 155
- Cosmetics and eczema, *Sept.*, 661
- Cough, action of diaphragm in, *Nov.*, 868
- after phrenicectomy, experimental data, *Nov.*, 871
- compressive phase, *Nov.*, 862, 864
- expulsive phase, *Nov.*, 862, 865
- in production of bronchiectasis, *Nov.*, 867
- inspiratory phase, *Nov.*, 862
- mechanics and physiology of, *Nov.*, 861
- Cowperitis, gonorrheal, *July*, 155
- Cramps and hypothyroidism, *Sept.*, 340
- Cretinism, *Sept.*, 355
- Cyanosis of newborn, diagnosis and treatment, *July*, 99
- Cystic mastitis, chronic, *Sept.*, 637
- Cystitis in children, *July*, 34
- DEFECATION, influence of indigestible residue on, *Sept.*, 453
- Dehydration fever in children, *July*, 47
- Dercum's syndrome, *Sept.*, 374
- Dermatitis, contact, *Sept.*, 651, 653
- Diabetes mellitus, borderline, *Sept.*, 346
- complicated by tuberculosis, treatment, *Nov.*, 829
- tolerance in, influence of tuberculosis on, *Nov.*, 836
- with hypothyroidism, *July*, 279
- Diaphragm, action of, in cough, 868
- Diaphragmatic pleurisy in children, *July*, 18
- Diarrhea, tuberculous, *Nov.*, 851, 855
- Diathesis, exudative, *Sept.*, 656
- Dick antitoxin, *July*, 314
- test, *July*, 312
- toxin, *July*, 313
- Diet in cardiovascular-renal disease, *July*, 214
- in constipation, *Sept.*, 449; 897
- in diabetes complicated by tuberculosis, *Nov.*, 830
- in myocardial insufficiency, 555
- in nutritional anemia in infancy, *Nov.*, 943
- in pulmonary tuberculosis, *Nov.*, with hemorrhage, *Nov.*, 811
- in secondary gastro-intestinal tuberculosis, *Nov.*, 886
- in tuberculosis of larynx, *Nov.*, 1029
- in uremia, *Sept.*, 529
- ketogenic, for urinary antiseptics, children, *Nov.*, 1029
- Digestive tract diseases in aged, 132
- Digitalis in myocardial insufficiency, *Sept.*, 549
- in rheumatic heart disease, *Nov.*, 811
- Diuretics in myocardial insufficiency, *Sept.*, 553
- in uremia, *Sept.*, 530
- Diverticula, esophageal, in aged, 132
- Drugs causing fever in children, 45
- Duodenal obstruction in newborn, *Sept.*, 621
- Dwarfism, *Sept.*, 353
- hypothyroid, *Sept.*, 356
- Paltauf, *Sept.*, 362
- Dysentery, amebic, in children, 24
- bacillary, in children, *July*, 24
- Dyspepsia in pulmonary tuberculosis, *Nov.*, 853
- Dyspituitarism, postencephalic, *July*, 229
- Dystonia, neurovegetative, *July*, 279
- Dystrophia adiposogenitalis, 374
- Dysuria in children, *Nov.*, 1036
- ECTOPIC pregnancy, *July*, 77
- Eczema, *Sept.*, 651
- Ecrematids, *Sept.*, 654

- Edema, cerebral, in newborn, *July*, 105, 109
- Embryonal adenomyosarcoma in children, *Nov.*, 1038
- Emphysema, early diagnosis and treatment, *Sept.*, 437
- Empyema, *July*, 329
- encapsulated, in children, *July*, 18
- tuberculous, *Nov.*, 841
- anaerobic, *Nov.*, 846
- pyogenic, *Nov.*, 845
- thoracoplasty in, *Nov.*, 848
- thoracotomy and aspiration in, *Nov.*, 843
- treatment, *Nov.*, 843
- with bronchial fistula, *Nov.*, 843, 845
- Encephalitis, clinical types, diagnosis and treatment, *Sept.*, 415
- epidemic, *Sept.*, 419
- dyspituitarism following, *July*, 229
- parkinsonism following, diagnosis and treatment, *July*, 223
- in children, *July*, 39
- toxic, *Sept.*, 415
- postvaccinal, *Sept.*, 430
- Encephalomyelitis, acute disseminated, associated with infections, *Sept.*, 430
- Endocarditis, subacute bacterial, in children, *July*, 57
- Endocervicitis, chronic, treatment, *July*, 119
- Endocrine disturbances, borderline, *Sept.*, 337
- in aged, *July*, 138
- infantilism, diagnosis and treatment, *Sept.*, 353
- obesity, *Sept.*, 369
- symposium, *Sept.*, 335
- Enemas in chronic constipation, *Nov.*, 903
- Enteritis, tuberculous, diet in, *Nov.*, 886
- Enterospasm, infantile, classification and treatment, *Sept.*, 511
- Enuresis and hypothyroidism, *Sept.*, 339
- in children, *Nov.*, 1036
- Epididymitis, gonorrheal, *July*, 150
- tuberculous, *Nov.*, 796, 801
- Erysipelas in aged, *July*, 137
- Erythema induratum of Bazin, *Nov.*, 1003
- nodosum, *Nov.*, 729
- Esophagus, obstruction, in newborn, *Sept.*, 617
- pressure diverticula, in aged, *July*, 132
- Estrogenic hormone therapy in acne vulgaris, *Nov.*, 988, 990
- in gonorrheal vaginitis, *Sept.*, 669, 675
- Exanthem subitum, *July*, 48
- Exercise in cardiac conditions, *July*, 191
- in chronic constipation, *Nov.*, 895
- Exophthalmic goiter, *July*, 285
- Extrasystoles, *July*, 177; *Sept.*, 540
- Exudative diathesis, *Sept.*, 656
- Fainting attacks and hypothyroidism, *Sept.*, 339
- Feeding, infant, in relation to vomiting in newborn, *Sept.*, 616
- Fever therapy in rheumatic heart disease, *Nov.*, 971
- Fevers in childhood, obscure origin, symposium on, *July*, 1
- Fibro-adenoma of breast, *Sept.*, 633
- Fibromyxoma of breast, *Sept.*, 636
- Fistula, bronchial, in tuberculous empyema, *Nov.*, 843, 845
- Floradex in gonorrheal vaginitis, *Sept.*, 674
- Fluoroscopy in pneumothorax therapy in tuberculosis, *Nov.*, 819
- Follicles, *Nov.*, 1003
- Folliculitis, gonorrheal, *July*, 153
- Food poisoning in children, *July*, 27
- residue, indigestible, influence on defecation, *Sept.*, 453
- method of isolating, *Sept.*, 450
- necessity in diet, *Sept.*, 455
- Foods, bulky, laxative value, *Sept.*, 449
- in chronic constipation, *Nov.*, 897
- Foreign body in lung, pulmonary bleeding in, *Sept.*, 488
- Fractures in aged, *July*, 138
- Froehlich's syndrome, *Sept.*, 374
- Functional disorders of children, diagnosis and treatment, *Sept.*, 581
- Fungus infections of lung, pulmonary bleeding in, *Sept.*, 488
- Fusospirochetosis of lung, pulmonary bleeding in, *Sept.*, 488
- GALLBLADDER, stoneless, diagnosis, *Sept.*, 471
- strawberry, *Sept.*, 473
- Galloping consumption, *Nov.*, 709
- in children, *Nov.*, 722
- Gallstones in aged, *July*, 144
- Gangrene of lung, pulmonary bleeding in, *Sept.*, 487
- Gastric analysis in pulmonary tuberculosis, *Nov.*, 856

- Gastro-enterospasm, infantile, classification and treatment, *Sept.*, 511
- Gastro-intestinal obstruction as cause of vomiting in newborn, *Sept.*, 617
- in pulmonary tuberculosis, *Nov.*, 851
- in diet and, *Nov.*, 886
- Gavage feeding of premature infant, *Nov.*, 956
- Genetic aspects of certain blood-system disorders, *July*, 253
- Genital tuberculosis associated with pulmonary tuberculosis, *Nov.*, 795, 808
- treatment, *Nov.*, 806
- Genito-urinary system, diseases, in aged, *July*, 134
- malignant disease of, *Nov.*, 1009
- Geriatrics, *July*, 127
- German measles, encephalitis in, *Sept.*, 433
- Gigantism, *Sept.*, 387
- Glandular fever in children, *July*, 55
- Goiter, toxic, *July*, 285
- Gonadotropic hormone therapy in acne vulgaris, *Nov.*, 988, 990
- Gonorrhea in male, complications, treatment, *July*, 147
- Gonorrheal arthritis, *July*, 152
- prostatitis, *July*, 150, 161
- vulvovaginitis, *July*, 123; *Sept.*, 665
- Graves' disease, *July*, 285
- Grippe, intestinal, *July*, 26
- Growth hormone therapy, *Sept.*, 365
- Gynecology, diagnostic mistakes, *July*, 75
- problems of family physician, symposium on, *July*, 59
- Habit vomiting in newborn, *Sept.*, 624
- Heart, alternation of, *July*, 188; *Sept.*, 545
- block, *July*, 185
- and hypothyroidism, *Sept.*, 339
- disease, in aged, *July*, 139
- physical exercise in, *July*, 191
- pulmonary bleeding in, *Sept.*, 489
- rheumatic, management, 961
- with cyanosis in newborn, *July*, 105, 111
- irregularities, diagnosis and treatment, *July*, 175
- significance, *Sept.*, 537
- premature contractions, *July*, 177
- Hematuria in children, *Nov.*, 1038
- in renal neoplasm, *Nov.*, 1010
- usual sources, *Nov.*, 1037
- Hemicellulose in foods, *Sept.*, 450
- Hemoglobin determination in nutritional anemia in infancy, *Nov.*, 934
- Hemoglobinuria, paroxysmal, *July*, 56
- Hemophilia, *July*, 258
- Hemoptysis, diagnosis and treatment, *Sept.*, 483
- Hemorrhage, cerebral, in newborn, *July*, 105, 109
- pulmonary, diagnosis and treatment, *Sept.*, 483
- in tuberculosis, diet in, *Nov.*, 886
- Herpes zoster, treatment, *July*, 239
- Hodgkin's disease in children, *July*, 54
- Hormone therapy in acne vulgaris, *Nov.*, 985, 990
- in gonorrheal vaginitis, *Sept.*, 669, 675
- in habitual abortion, *July*, 96
- in hypopituitarism, *Sept.*, 384
- in infantilism, *Sept.*, 360, 364, 365
- in sterility, *July*, 70
- Hydronephrosis in children, *Nov.*, 1039
- Hyperinsulinism, diagnosis and treatment, *Sept.*, 393
- Hyperpituitarism, treatment, *Sept.*, 386
- Hypertension in cardiovascular-renal disease, *July*, 209
- Hyperthyroidism, *July*, 285
- borderline cases, *Sept.*, 342
- with normal metabolic rate, *Sept.*, 344
- Hypoglycemia of hyperinsulinism, *Sept.*, 393, 402
- differentiation from other states of hypoglycemia, *Sept.*, 404
- spontaneous, *Sept.*, 347
- Hypoglycemic insulin reactions in tubercular diabetics, *Nov.*, 834
- Hypogonadism, primary, *July*, 68
- Hypopituitarism, treatment, *Sept.*, 379
- Hypothyroid infantilism, *Sept.*, 356
- Hypothyroidism, borderline cases, *Sept.*, 337
- in diabetes mellitus, *July*, 279
- ICTERO-ANEMIA, hemolytic, genetic aspects, *July*, 256
- Impedance angle in hyperthyroidism, *July*, 287
- Incubator for premature infant, *Nov.*, 952
- Infantile colic, classification and treatment, *Sept.*, 511
- Infantilism, endocrine, diagnosis and treatment, *Sept.*, 353
- Infections, acute, in aged, *July*, 137
- encephalitis following, *Sept.*, 430
- in newborn, vomiting due to, *Sept.*, 622



- Inflammatory diseases of breast, *Sept.*, 627  
 pelvic, ectopic pregnancy and, *differentiation, July*, 77  
 Influenza, encephalitis following, *Sept.*, 437  
 in children, fever in, *July*, 18  
 Inguinal lymphadenitis in gonorrhea in male, *July*, 156  
 Injuries of lung, pulmonary bleeding in, *Sept.*, 487  
 Insulin in diabetes complicated by tuberculosis, *Nov.*, 832  
 reactions, *Nov.*, 834  
 Intestinal gripe, *July*, 26  
 obstruction in aged, *July*, 133  
 tuberculosis in children, *July*, 21  
 secondary, *Nov.*, 851  
 diet in, *Nov.*, 886  
 Iodized oil, intratracheal injection, in asthma, analysis of 1000 cases, *Nov.*, 907  
 Iodine, blood, in hyperthyroidism, *July*, 286  
 Iron preparations in nutritional anemia in infants, *Nov.*, 937  
 Irritability and hypothyroidism, *Sept.*, 339
- JAPANESE type B encephalitis, *Sept.*, 423  
 Jaundice, epidemic, in children, *July*, 29
- KETOGENIC diet for urinary antiseptics in children, *Nov.*, 1029
- Kidney, abscesses, multiple, in children, *July*, 33  
 carbuncle, in children, *July*, 33  
 embryonal adenomyosarcoma, *Nov.*, 1038  
 infections, pyuria in children due to, *Nov.*, 1028  
 malignant disease, diagnosis, *Nov.*, 1010  
 stones in, in children, *Nov.*, 1035  
 tuberculosis, associated with pulmonary tuberculosis, *Nov.*, 787, 807  
 in children, *July*, 34; *Nov.*, 1036  
 tumors, in children, *July*, 34; *Nov.*, 1017, 1038  
 Wilms' tumor, *Nov.*, 1017, 1038
- LARYNX, tuberculosis, diet in, *Nov.*, 887  
 Laxatives in chronic constipation, *Nov.*, 902
- Lead encephalitis, *Sept.*, 417  
 Lethargic encephalitis, *Sept.*, 419  
 Leukemia in children, *July*, 54  
 Lichen scrofulosorum, *Nov.*, 1003  
 Lignin in foods, *Sept.*, 450  
 Lipiodol, intratracheal injection, in asthma, *Nov.*, 907  
 Lipomatoses, *Sept.*, 378  
 Liver, enlargement, diseases associated with, diagnosis, *July*, 295  
 feeding in nutritional anemia in infants, *Nov.*, 948  
 Lobectomy in pulmonary hemorrhage, *Sept.*, 492  
 Lorain-Levi infantilism, *Sept.*, 362  
 Lung, abscesses, multiple, in children, *July*, 18  
 hemorrhage from, diagnosis and treatment, *Sept.*, 483  
 diseases, in aged, *July*, 135  
 tuberculosis. See *Tuberculosis, pulmonary.*  
 Lupus miliaris disseminatus, *Nov.*, 1004  
 pernio, *Nov.*, 1004  
 vulgaris, *Nov.*, 1002  
 Luxus consumption, *Sept.*, 365  
 Lymph nodes, mesenteric, tuberculosis of, *July*, 22  
 Lymphadenitis, cervical, as cause of fever in children, *July*, 14  
 inguinal, in gonorrhea in male, *July*, 156  
 Lymphangitis, gonorrheal, in male, *July*, 156
- MALARIA in children, *July*, 53  
 inoculata, *July*, 53  
 Malignant disease of genito-urinary tract, diagnosis, *Nov.*, 1009  
 Malpositions of uterus, diagnostic mistakes, *July*, 79  
 Malta fever, *July*, 51  
 Mantoux test, *Nov.*, 730  
 Marasmus, chlorotic, *Nov.*, 982  
 Massage in chronic constipation, *Nov.*, 896  
 Mastitis, cystic, chronic, *Sept.*, 637, 641  
 pyogenic, acute, *Sept.*, 627  
 chronic, *Sept.*, 630  
 tuberculous, *Sept.*, 630  
 Mastoiditis as cause of fever, *July*, 15  
 Measles, encephalitis in, *Sept.*, 432  
 Mediastinal abscess in children, *July*, 19  
 infection, as cause of fever in children, *July*, 18  
 Meningitis, acute aseptic, *July*, 41

- Meningitis, acute lymphocytic, *July*, 40  
     serous, *Sept.*, 438  
     meningococcic, *July*, 35  
     miscellaneous forms, *July*, 38  
     syphilitic, *July*, 42  
     tuberculous, *July*, 37  
Menopause, abnormal bleeding before and after, causes, *July*, 83  
Menstruation, vicarious, from lungs, *Sept.*, 490  
Mesenteric lymph nodes, tuberculosis of, *July*, 22  
Metabolism, basal, in hyperthyroidism, *July*, 288  
Miliary tuberculosis, hematogenous, diffusely disseminated, *Nov.*, 760  
Milk mixtures, simple, for premature infant, *Nov.*, 951  
Mineral oil in constipation, *Nov.*, 901  
Miscarriage, diagnostic mistakes in, *July*, 76  
     persistent, *July*, 81  
Mönckeberg's sclerosis, *July*, 130  
Mononucleosis, acute infectious, *July*, 55  
Morbus coeruleus, *July*, 106  
Mumps, encephalitis in, *Sept.*, 436  
Muscular pains and hypothyroidism, *Sept.*, 340  
Myocardial insufficiency, treatment, *Sept.*, 547  
Myxoma, intracanalicular, of breast, *Sept.*, 636  
  
NANOSOMIA hypothyrotica, *Sept.*, 361  
Nasal septum, ulcer of, and hypothyroidism, *Sept.*, 338  
Nausea in pulmonary tuberculosis, *Nov.*, 854  
Neocarsphenamine in herpes zoster, *July*, 248  
Nephrosclerosis in aged, *July*, 134  
Neuroblastoma of adrenal, *Nov.*, 1039  
Neurocirculatory asthenia simulating hyperthyroidism, *Sept.*, 343  
Neuroses from general practitioner's viewpoint, *Sept.*, 559  
Newborn, cyanosis of, *July*, 99  
     sepsis of, *July*, 47  
     vomiting in, *Sept.*, 615  
Nursing care of premature infant, *Nov.*, 951  
Nutritional anemia in infancy, management, *Nov.*, 933  
  
OBESITY and hypothyroidism, *Sept.*, 339  
     endocrine, *Sept.*, 369  
     exogenous, *Sept.*, 376  
  
Obstetric problems of family physician, symposium on, *July*, 59  
Occupational therapy in myocardial insufficiency, *Sept.*, 557  
Oculogyric crises, *July*, 228; *Sept.*, 422  
Oertel terrain exercises, *July*, 203  
Old age, diseases of, *July*, 127, 131  
Ornstein's triad, *July*, 254  
Osteomyelitis in children, *July*, 49  
Otitis media, fever due to, *July*, 15  
Ovalocytosis, *July*, 257  
Ovarian failure, primary, *July*, 68  
  
PAGET's disease in aged, *July*, 138  
Pain, abdominal, in pulmonary tuberculosis, *Nov.*, 854  
     in urologic disease in children, *Nov.*, 1038  
Paltauf dwarfism, *Sept.*, 362  
Pancreatitis, acute, in children, *July*, 26  
Parafrenal sinusitis in gonorrhea, *July*, 158  
Paraphimosis, gonorrheal, *July*, 157  
Paratyphoid fever in children, *July*, 23  
Parkinsonism, *Sept.*, 422  
     incipient, diagnosis and treatment, *July*, 223  
Paroxysmal tachycardia, *Sept.*, 544  
Parrot fever, *July*, 56  
Pastia's sign, *July*, 309  
Patch tests in eczema, *Sept.*, 659  
Pel-Ebstein Hodgkin's disease, *July*, 54  
Pelvic inflammatory disease, ectopic pregnancy and, differentiation, *July*, 77  
Peptic ulcer, *Sept.*, 461  
Periarteritis nodosa, clinical aspects, *Nov.*, 973  
Pericarditis, rheumatic, *Nov.*, 968  
Perinephric abscess in children, *July*, 33  
Peritonitis in children, fever in, *July*, 25  
     tuberculous, in children, *July*, 22  
Pertussis, encephalitis in, *Sept.*, 436  
Phenobarbital in infantile colic, *Sept.*, 517, 522  
Phimosis, inflammatory, in gonorrhea, *July*, 156  
Phlebitis, dorsal, gonorrheal, *July*, 156  
Phrenic nerve injury in newborn, *July*, 105, 110  
Phrenicectomy, cough after, experimental data, *Nov.*, 871  
Phyone, *Sept.*, 360, 364, 384  
Physical exercise in cardiac conditions, *July*, 191  
Pill-rolling tremor, *July*, 232

- Pirquet test, *Nov.*, 730  
 Pituitary basophilism, *Sept.*, 349, 387  
   hyperfunction, treatment, *Sept.*, 379  
   infantilism, *Sept.*, 362  
   insufficiency in sterility, *July*, 67  
   treatment, *Sept.*, 379  
 Pituitrin in herpes zoster, *July*, 246  
 Pleurisy, acute, treatment, *July*, 323  
 diaphragmatic, in children, *July*, 18  
 Pneumoconiosis, pulmonary bleeding in, *Sept.*, 488  
 Pneumectomy in pulmonary hemorrhage, *Sept.*, 492  
 Pneumonia, caseous, tuberculous, *Nov.*, 709, 744  
   in aged, *July*, 136  
   in children, fever in, *July*, 17  
   pulmonary bleeding in, *Sept.*, 488  
 Pneumonolysis, closed, in far advanced tuberculosis, *Nov.*, 777  
 Pneumothorax, artificial, in pulmonary hemorrhage, *Sept.*, 492  
   for far advanced tuberculosis, *Nov.*, 775  
   for pulmonary tuberculosis, fluoroscopy and x-ray in, *Nov.*, 819  
   spontaneous, in tuberculosis, *Nov.*, 715  
 Poliomyelitis, *July*, 38  
 Postmenopausal bleeding, causes, *July*, 88  
 Postural emphysema, *Sept.*, 442  
 Pregnancy, and hypertension, *July*, 221  
   ectopic, pelvic inflammatory disease and, differentiation, *July*, 77  
   pulmonary tuberculosis and, *Nov.*, 811  
 Premature infant, care and feeding of, with special reference to simple milk mixtures, *Nov.*, 951  
 Premenopausal bleeding, causes, *July*, 85  
 Prephysin, *Sept.*, 386  
 Prostate, carcinoma of, diagnosis, *Nov.*, 1022  
   tuberculosis of, *Nov.*, 796, 799, 800  
 Prostatic hypertrophy, *July*, 135  
 Prostatitis, chronic, management, *July*, 161  
   foci of infection in, *July*, 168  
   gonorrheal, *July*, 150, 161  
 Pruritus in uremia, treatment, *Sept.*, 533  
 Psittacosis, *July*, 56  
 Psychoses from general practitioner's viewpoint, *Sept.*, 559  
   in aged, *July*, 140  
 Pulsus alternans, *July*, 188  
 Purpura in children, *July*, 57  
 Pyelitis in children, fever due to, *July*, 31  
   pyuria due to, *Nov.*, 1028  
 Pyelography in renal neoplasm, *Nov.*, 1013  
 Pyelonephritis, acute, pyuria in children due to, *Nov.*, 1028  
 Pyloric obstruction in newborn, *Sept.*, 618  
 Pyridium therapy in gonorrheal vaginitis, *Sept.*, 672  
 Pyuria in children, *Nov.*, 1028  
   fever due to, *July*, 31  
 RABIES inoculations, encephalitis following, *Sept.*, 435  
 Rat-bite fever, *July*, 52  
 Rectal constipation, treatment, *Nov.*, 895  
 Relapsing fever, *July*, 53  
 Renal. See *Kidney*.  
 Renal-cardiovascular disease, preventive aspects, *July*, 209  
 Respiratory disorders in parkinsonism, *July*, 229  
   infections, encephalitis following, *Sept.*, 437  
   lower, in children, fever due to, *July*, 17  
   upper, in children, fever due to, *July*, 9  
 Retropharyngeal abscess as cause of fever in children, *July*, 13  
 Rheumatic fever in children, *July*, 27, 50  
   heart disease, management, *Nov.*, 961  
 Riedel's lobe, *July*, 299  
 Rocky Mountain spotted fever, *July*, 52  
 Roentgen diagnosis of renal neoplasm, *Nov.*, 1013  
   of silicosis, *Sept.*, 505  
   of stoneless gallbladder, *Sept.*, 474  
   examination in pneumothorax therapy of tuberculosis, *Nov.*, 819  
   treatment of herpes zoster, *July*, 244  
 Roseola infantum, *July*, 48  
 Rumpel-Leede's sign, *July*, 309  
 SARCOID of Boeck, *Nov.*, 1004  
   of Darier-Roussy, *Nov.*, 1001  
 Scarlet fever, *July*, 307  
 Schultz-Charlton reaction, *July*, 315  
 Sclerosis, Monckeberg's, *July*, 130  
 Scrofuloderma, *Nov.*, 1002  
 Scrofulosis, *Nov.*, 729  
 Scurvy in children, *July*, 49

- Seminal vesicles, tuberculosis of, *Nov.*, 802  
 vesiculitis in gonorrhea, *July*, 154  
 Senescence, changes of, *July*, 128  
 Sepsis of newborn, *July*, 47  
 Sicklemia, *July*, 55  
 genetic aspects, *July*, 258  
 Silicosis, diagnosis and prevention, *Sept.*, 497  
 Simmonds' disease, *Sept.*, 383  
 Sinus arrhythmia, *Sept.*, 540  
 infection, paranasal, fever due to, *July*, 11  
 Sinusitis, parafrenal, in gonorrhea, *July*, 158  
 Skin, tuberculosis of, *Nov.*, 995  
 Smallpox, encephalitis in, *Sept.*, 433  
 Sodium iodide in herpes zoster, *July*, 247  
 Spherocytes, *July*, 256  
 Splenomegaly, diseases associated with, diagnosis, *July*, 295  
 Sputum in secondary gastro-intestinal tuberculosis, *Nov.*, 856  
 St. Louis type encephalitis, *Sept.*, 424  
 Stenosis, pyloric, in newborn, *Sept.*, 618  
 Sterility in female, *July*, 63  
 in male, *July*, 61  
 Stokes-Oertel terrain exercises, *July*, 203  
 Stools in pulmonary tuberculosis, *Nov.*, 857  
 Strawberry gallbladder, *Sept.*, 473  
 Stricture, ureteral, congenital, *Nov.*, 1033  
 Subphrenic abscess in children, *July*, 26  
 Syphilitic meningitis in children, *July*, 42  
  
 TACHYCARDIA, paroxysmal, *July*, 179;  
*Sept.*, 544  
 Teeth, abscessed, in children, *July*, 48  
 Teething, fever due to, *July*, 48  
 Telangiectasia, hereditary hemorrhagic, *July*, 257  
 Testis, atrophy of, *Nov.*, 1023  
 Testicle, malignant disease, diagnosis, *Nov.*, 1023  
 tuberculosis of, *Nov.*, 802  
 undescended, *Nov.*, 1039  
 Tetany in newborn, *July*, 112  
 Thoracentesis in pleurisy, *July*, 328  
 Thoracoplasty in tuberculous empyema, *Nov.*, 848  
 Thoracotomy in tuberculous empyema, *Nov.*, 843  
 Thymus enlargement in newborn, *July*, 107, 111  
 Thyroid eczema, *Sept.*, 657  
 Thyrotoxicosis, hypoglycemia with, *Sept.*, 405  
 Tonsils, infected, and fever, *July*, 10  
 Trauma in production of eczema, *Sept.*, 653  
 Tremor, pill-rolling, *July*, 232  
 Trichomonas vaginalis vaginitis, treatment, *July*, 125  
 Tubercle, *Nov.*, 1000  
 anatomic, *Nov.*, 1002  
 Tuberculids, *Nov.*, 998  
 papulonecrotic, *Nov.*, 1003  
 rosacea-like, *Nov.*, 1003  
 Tuberculin tests, *Nov.*, 730  
 Tuberculoderms, *Nov.*, 995  
 Tuberculoid, *Nov.*, 1000  
 Tuberculosis colliquativa, *Nov.*, 1002  
 galloping, *Nov.*, 709  
 in children, *Nov.*, 723  
 gastro-intestinal, secondary, *Nov.*, 851  
 diet in, *Nov.*, 886  
 genital, associated with pulmonary tuberculosis, *Nov.*, 795, 808  
 treatment, *Nov.*, 806  
 indurative, *Nov.*, 1003  
 intestinal, *Nov.*, 851, 886  
 in children, *July*, 21  
 lichenoides, *Nov.*, 1003  
 luposa, *Nov.*, 1002  
 miliary, hematogenous, diffusely disseminated, *Nov.*, 760  
 of epididymis, *Nov.*, 796, 801  
 of kidney, associated with pulmonary tuberculosis, *Nov.*, 787, 807  
 in children, *July*, 34; *Nov.*, 1036  
 of larynx, diet in, *Nov.*, 887  
 of mesenteric lymph nodes, *July*, 22  
 of prostate, *Nov.*, 796, 799, 800  
 of seminal vesicles, *Nov.*, 802  
 of skin, *Nov.*, 995  
 of testis, *Nov.*, 802  
 papulonecrotica, *Nov.*, 1003  
 pulmonary, acinous nodose, *Nov.*, 706  
 caseous pneumonia in, *Nov.*, 709, 744  
 cavity formation and healing, *Nov.*, 710  
 chronic hematogenous, *Nov.*, 715, 767  
 productive, *Nov.*, 750  
 clinical forms, recognition and treatment, *Nov.*, 737  
 closed pneumonolysis for, *Nov.*, 777  
 collapse therapy, *Nov.*, 775  
 fluoroscopy and x-ray in, *Nov.*, 819

- Tuberculosis, pulmonary, cough in, mechanics and physiology of, *Nov.*, 861  
 diabetes complicating, treatment, *Nov.*, 829  
 diet prescription for, *Nov.*, 877  
 exudative benign, *Nov.*, 740  
   productive, *Nov.*, 749  
 far advanced, management, *Nov.*, 775  
 gastro-intestinal symptoms, *Nov.*, 851  
   diet in, *Nov.*, 886  
 genital tuberculosis associated with, *Nov.*, 795, 808  
 hematogenous, *Nov.*, 759  
   acute miliary, *Nov.*, 760  
   chronic, *Nov.*, 715, 767  
 hemorrhage in, *Sept.*, 485  
   diet for, *Nov.*, 886  
 in aged, *July*, 136  
 in children, *July*, 19; *Nov.*, 719  
   diagnosis and symptoms, *Nov.*, 726  
   dissemination, *Nov.*, 722  
   primary focus, *Nov.*, 690, 720  
   prognosis, prophylaxis, and therapy, *Nov.*, 734  
   stage of generalization, *Nov.*, 732  
   tuberculin tests, *Nov.*, 730  
 influence on diabetic tolerance, *Nov.*, 836  
 isolated, *Nov.*, 702  
 pathology and pathogenesis, *Nov.*, 689  
 pneumothorax for, *Nov.*, 775  
   fluoroscopy and x-ray in, *Nov.*, 819  
 pregnancy and, *Nov.*, 811  
 primary complex, *Nov.*, 689  
   lymph nodes of, *Nov.*, 696  
   focus, *Nov.*, 690, 720  
 renal tuberculosis associated with, *Nov.*, 787, 807  
 spontaneous pneumothorax in, *Nov.*, 715  
   stage of generalization, *Nov.*, 697  
 urogenital, associated with pulmonary tuberculosis, *Nov.*, 787  
 verrucosa cutis, *Nov.*, 1002  
 Tuberculous empyema, *Nov.*, 841.  
   See also *Empyema*.  
   enteritis, diet in, *Nov.*, 886  
   mastitis, *Sept.*, 630  
   meningitis in children, *July*, 37  
   peritonitis in children, *July*, 22  
 Tularemia, *July*, 51  
 Tumors, adrenal cortical, *Sept.*, 349  
   malignant, of genito-urinary tract, *Nov.*, 1009  
   Tumors of brain in children, *July*, 46  
     of breast, *Sept.*, 633  
     of kidney in children, *July*, 34  
       *Nov.*, 1017, 1038  
     urologic, in children, *Nov.*, 1038  
   Typhoid fever in children, *July*, 23  
   Typhus fever, *July*, 52  
 ULCER of nasal septum and hypothyroidism, *Sept.*, 338  
   peptic, *Sept.*, 461  
   tuberculous, *Nov.*, 1002  
 Undescended testicle, *Nov.*, 1039  
 Undulant fever in children, *July*, 51  
 Uremia, treatment, *Sept.*, 527  
 Ureter, calculi, in children, *Nov.*, 1034  
   malignant disease, *Nov.*, 1021  
   stricture, congenital, *Nov.*, 1033  
 Urethritis, gonorrheal, in male, *July*, 147  
 Urinary antiseptics for children, *Nov.*, 1028  
   obstruction, pyuria in children due to, *Nov.*, 1030, 1032  
   tract, malignant disease, diagnosis, *Nov.*, 1009  
 Urination, disturbances of, in children, *Nov.*, 1036  
 Urogenital tuberculosis associated with pulmonary tuberculosis, *Nov.*, 787  
 Urography in renal neoplasm, *Nov.*, 1013  
 Urologic conditions, common, in children, *Nov.*, 1027  
 Uterus, malpositions, diagnostic mistakes, *July*, 79  
 VACCINATION, encephalitis following, *Sept.*, 430, 433  
 Vaginal bleeding, abnormal, pre- and postmenopausal, causes, *July*, 83  
   discharges, diagnosing, *July*, 80  
 Vaginitis, gonorrheal, treatment, *July*, 123; *Sept.*, 665  
 Vagotonia, hypoglycemia in, *Sept.*, 404  
 Vascular disease, hypertensive, *July*, 209  
 Verruca necrogenica, *Nov.*, 1002  
 Vesiculitis, seminal, in gonorrhea, *July*, 154  
 Vicarious menstruation from lungs, *Sept.*, 490  
 Vitamins, rôle in nutritional anemia, *Nov.*, 949  
 Vomiting in newborn, *Sept.*, 615  
   in pulmonary tuberculosis, *Nov.*, 854  
   uremic, treatment, *Sept.*, 534

- |   |   |
|---|---|
| Von Economo encephalitis, <i>Sept.</i> , 419                  | Whooping cough, encephalitis in, <i>Sept.</i> , 436 |
| Von Gierke's disease, infantilism in, <i>Sept.</i> , 355      | Wilms' tumor, <i>Nov.</i> , 1017, 1038              |
| Vulvovaginitis, different types, treatment, <i>July</i> , 122 |   |
| gonorrheal, treatment, <i>Sept.</i> , 665                     | YEAST vulvovaginitis, treatment, <i>July</i> , 124  |
| WATER, plentiful, in chronic constipation, <i>Nov.</i> , 896  |   |
| Weil's disease, <i>July</i> , 29                              | ZOSTER ophthalmicus, <i>July</i> , 240              |
|   | oticus, <i>July</i> , 240                           |









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# CONTENTS

	PAGE
SYMPOSIUM ON RELIEF OF PAIN.....	1013
<i>Relief of Headaches, Facial Neuralgia, Glossopharyngeal Neuralgia, Superior Laryngeal Neuralgia, Occipital Neuralgia, Pain from Sluder's Neuralgia</i> .....	1015
By DR. ABRAHAM ETTLESON	
Relief of Lumbago and Sciatica.....	1033
By DR. ROBERT O. RITTER	
Treatment of Earache.....	1039
By DR. LOUIS T. CURRY	
Pain in the Dental Field.....	1057
By DR. CHARLES W. FREEMAN	
Relief for Painful Feet.....	1067
By DR. WALTER R. FISCHER	
Pain Simulating That Produced by Coronary Disease .....	1077
By DR. G. K. FENN	
Treatment of Angina Pectoris.....	1085
By DR. N. C. GILBERT	
Pain in the Abdomen: Clinical Significance and Consideration of Relief... ..	1113
By DR. LOWELL D. SNORF	
Relief of Pain Arising in the Female Pelvis... ..	1131
By DR. J. P. GREENHILL	
Septic Sore Throat: Clinical and Bacteriological Considerations... ..	1143
By DR. ISADORE PILOT	
The Treatment of Sepsis and Pyemia Following Tonsillar Infections .....	1151
By DR. SAMUEL J. PEARLMAN	
Jaundice: A Brief Discussion of Diagnosis Followed by a Proposed Medical Management.....	1163
By DR. CLARENCE F. G. BROWN	
The Treatment of Bronchiectasis.....	1171
By DR. JEROME HEAD	
Therapeutic Value of Prostatic Massage: With a Discussion on Prostatitis and the Significance of Proper Rectal Palpation of the Prostate Gland.....	1181
By DR. VINCENT J. O'CONOR	
The Value of Eye Symptoms in the Diagnosis of General Disease.....	1187
By DR. RICHARD J. TYNNEN	
Ringworm of the Scalp.....	1241
By DR. MICHAEL HIGGINS EBERT	
Gastro-Intestinal Manifestations of Systemic Disease and Their Differential Diagnosis.....	1251
By DR. SIDNEY A. PORTIS	
Treatment of Coma.....	1265
By DRS. SOLOMON STROUSE and HERBERT F. BINSWANGER	
Venous Pressure.....	1273
By DR. WILLIAM A. BRAMS	
The Immunization of Infants and Young Children Against Infectious Diseases .....	1277
By DR. HEYWORTH N. SANFORD	
Rickets: Is There a Dietetic Factor?.....	1291
By DRS. JESSE R. GERSTLEY and MEYER TEITELBAUM	
Cumulative Index. . .	1305

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# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON RELIEF OF PAIN

IN a recent number of the Medical Clinics there was a Symposium on Pain. In this issue we have carried the thought a little further and have gathered a group of clinics on the Relief of Pain. It has been our endeavor to cover the regions of the body in which the relief of pain is the problem of the general practitioner.

The following clinics are included in this Symposium:

Abraham Ettleson: RELIEF OF HEADACHES, FACIAL NEURALGIA, GLOSSOPHARYNGEAL NEURALGIA, SUPERIOR LARYNGEAL NEURALGIA, OCCIPITAL NEURALGIA, PAIN FROM SLUDER'S NEURALGIA.

Robert O. Ritter: RELIEF OF LUMBAGO AND SCIATICA.

Louis T. Curry: TREATMENT OF EARACHE.

Charles W. Freeman: PAIN IN THE DENTAL FIELD.

Walter R. Fischer: RELIEF FOR PAINFUL FEET.

G. K. Fenn: PAIN SIMULATING THAT PRODUCED BY CORONARY DISEASE.

N. C. Gilbert: TREATMENT OF ANGINA PECTORIS.

Lowell D. Snorf: PAIN IN THE ABDOMEN: CLINICAL SIGNIFICANCE AND CONSIDERATION OF RELIEF.

J. P. Greenhill: RELIEF OF PAIN ARISING IN THE FEMALE PELVIS.



## CLINIC OF DR. ABRAHAM ETTLESON

LOYOLA UNIVERSITY

### RELIEF OF HEADACHES, FACIAL NEURALGIA, GLOSSO-PHARYNGEAL NEURALGIA, SUPERIOR LARYNGEAL NEURALGIA, OCCIPITAL NEURALGIA, PAIN FROM SLUDER'S NEURALGIA

#### RELIEF OF HEADACHES

THE clinic today concerns itself mainly with the relief of headache due to migraine. It is to be understood that the following outline of treatment is intended only for those patients in whom a diagnosis of migraine is made after all other causes of headache have been excluded. For a general discussion of migraine the reader is referred to the literature on that subject.

In order to obtain relief from this distressing affliction, it is necessary to avoid possible precipitating or exciting causes of attacks of migraine such as fatigue, mental or physical, continued worries, fears and excitement, indiscretions of eating, drinking or smoking, and exposure. In a positive direction, the sufferers from migraine should adhere to a regular hygiene of living with regulation of diet and bowels, abundance of fresh air, sleep, and light daily exercise. On general medical principles physical defects should be corrected, although their correction may not bring relief from the headaches. Likewise the removal of foci of infection and the cure of constipation may fail to produce the desired results.

With recent advances in allergic and endocrine disorders, treatment for the relief of migraine has been undertaken by specialists in these fields with reported variable success.



Among the allergic disorders food disagreements have been blamed for the periodic headaches, for which skin tests are made, and "elimination diets" are given, or protein desensitization with peptone or other nonspecific protein is done. In the endocrine field various drugs from the selection of organotherapy are employed, particularly theelin one ampule every other day for one week before regular menstrual periods, and placental hormone (emmenin), an emmenagogue, or gynergen before menstruation. The rationale for the use of these drugs is the frequent association of attacks of migraine with the menstrual period. It is wise not to promise the sufferer relief from these measures, for failures from these forms of treatment are common; and promise unfulfilled, confidence is lost.

Regarding the use of drugs for the relief of migraine many have been tried, but none is specific for the disease. Among them the two which have received the most credit for affording relief are fluid extract of *Cannabis indica* in the largest dosage tolerated, starting with 2 minims every four hours, and sodium thiosulphate 15 grains intravenously. The former probably produces its desirable effects by depressing the sensory pathways in the spinal cord, and, in large doses, producing sleep. The favorable influence of thiosulphate on headache is not understood. The bromides, luminal, calcium salts, salicylates, and caffeine have been tried, each alone or in combination, with varying results, but on the whole they have not been successful. Morphine is to be avoided, or used only as a last resort, because of the danger of addiction.

Ligation of the middle meningeal artery on one or both sides is being done today after all palliative measures have been tried and failed. In the few reported operated cases and in those known to me, the ligation effected relief from the severe headaches. The operation, which is only slightly more than a subtemporal decompression, can be done under local anesthesia in the upright position. It is a relatively simple and short procedure, practically entirely devoid of risk.

The reason for the success of this procedure is explained by the theory that migraine headaches are caused by vaso-

motor spasm of cerebral and meningeal vessels brought on by an irritative affection of the cervical sympathetic ganglia. This supposition is rendered plausible by the recent demonstration of nerve fibers in cerebral vessels. Spasms of the latter produce the various visual disturbances, aphasia, paresthasias, and psychic phenomena of migraine, while constriction of the meningeal vessels is thought to be the cause of the severe hemicrania through the involvement of the sympathetic plexus encircling the latter. Hence, severing the artery destroys the sympathetic plexus around it, thus preventing spasm of the vessel. On the other hand, avulsion of the sensory root of the gasserian ganglion on the affected side has not brought relief from migraine headaches.

For the relief of an attack "nearly every patient has his own pet remedy" (P. Bassoe). A hot mustard foot bath, or a warm full bath, followed by rest in bed in a quiet, darkened room with warm compresses to the head and eyes may afford relief from the intense headache. One or more of the coal tar products—phenacetin, aspirin, pyramidon, each in 5 grain doses, and inhalation of the contents of a pearl of amyl nitrite may be effective.

#### RELIEF OF FACIAL NEURALGIA

We shall consider here chiefly the relief of trigeminal, or, as commonly called, trifacial neuralgia. All other causes of pain in the face must be looked for and excluded before diagnosis of *tic douloureux* is made. In this regard it is particularly important to distinguish between *psychalgia* and true paroxysms of trigeminal neuralgia. In the latter condition the pain always occurs in paroxysms and is limited to the true anatomical distribution of the fifth nerve on one side, never spreading across the midline or beyond the nerve area, while in the former the pain may be continuous and located anywhere in the face, head and neck, or shoulders.

Having determined that the pain in the face is due to major *tic*, relief may be obtained by one of several procedures. Since one of the cardinal features of trifacial neuralgia is the presence of hyperesthetic areas or trigger zones on the face,

scalp, or in the mouth which when touched set off a paroxysm, the sufferer will have learned from painful experience to leave these tender points absolutely untouched. He will therefore refrain from rubbing his eyes, touching, washing and wiping his face or lips, combing his hair, brushing his teeth, laughing, talking, blowing his nose, sneezing, coughing, or moving his jaw, according to the branch of the fifth nerve affected. He will also have learned to avoid cold drafts and chill, excitement and noises.

As in migraine, here also on general medical principles all possible local causes of pain in the face, as infected teeth or nasal sinuses, should be treated, although no relief may follow. By the time the patient will have drifted into the hands of a neurologist or neurosurgeon, the victim already will have sacrificed most or all of his sound teeth and submitted to one or more operations on his nose and sinuses without avail.

For temporary relief of pain deep inhalation of 20 to 30 drops of trichlorethylene (chlorylen) poured on a piece of gauze while patient reclines on one side is recommended. This drug acts selectively on the fifth nerve. All other drugs including morphine are worthless in the treatment of this affliction.

Roentgen radiation over the gasserian ganglion has lately been tried, but the fact that it has not displaced other measures after several years of trial indicates the limited efficacy of this procedure. However, postherpetic neuralgic pain is relieved by this method but not by operation.

Alcohol injection into the nerve trunks was the best known method of treatment until surgery began to be employed for the relief of facial pain. This method is still useful in many cases, especially in those in whom surgery is contraindicated. It is for the benefit of these cases that the technic of alcohol injection is here given in detail. Alcohol injection offers only temporary relief, the pain recurring in from six months to a few years. It is always advisable to inform the patient about the numbness of the face that follows injection.

The *modus operandi* of alcohol when injected into a nerve

explains the reason for only temporary relief from pain. Alcohol when injected into the nerve causes destruction by coagulation of the nerve fibers at the site of injection followed by degeneration of the nerve elements *below* this point to the periphery. The injection, which is excessively painful over the area supplied by the nerve, produces anesthesia almost immediately. So long as the nerve fiber *above* the point of injection and its nerve cell of origin within the ganglion are intact, a new nerve fiber will commence to grow downward from the cell body during the process of nerve regeneration, and by this means the damaged nerve is renewed and its conduction powers are re-established after an interval varying from six months to two years. Injection of the gasserian ganglion may offer permanent relief, but it is fraught with great danger except in the hands of a highly skilled operator. The alcohol might enter the optic nerve and produce blindness, or the oculomotor nerves and cause paralysis, or the cavernous sinus resulting in thrombosis. It makes later resection of the sensory root much more difficult. It may lead to corneal ulceration just as resection of the sensory root, and hence has no advantage over the latter procedure. In short, injection of the gasserian ganglion is not recommended.

Furthermore, an excellent knowledge of the anatomy of the trigeminal nerve is necessary to be successful with alcohol injection for the relief of tic douloureux. The depth to which the needle must be inserted in the tissues is very important, and can be determined by placing a small piece of rubber on the needle (Fig. 115) before insertion to the estimated depth of the nerve to be injected. The surest sign that the needle is in the correct position is the occurrence of pain in the area supplied by that nerve. The point of the needle must puncture the nerve trunk so that the alcohol actually penetrates among the nerve fibers.

The needles used are of stainless steel and flexible, like the kind employed in local infiltration anesthesia. The skin at the site of injection is made antiseptic in the usual manner. The alcohol is *never* injected into the nerve until anesthesia

has resulted from injecting a few drops of 2 per cent novocain. The syringe with novocain is then replaced by one with 95 per cent alcohol and the nerve is injected with it one drop at a time until the area of the nerve is totally anesthetic to pain, and there is no longer felt a burning sensation in the cutaneous distribution of the nerve.

**Neuralgia of the First Division.**—*Technic for Injection of the Supra-orbital Nerve.*—(Figs. 111, 112.) The supra-

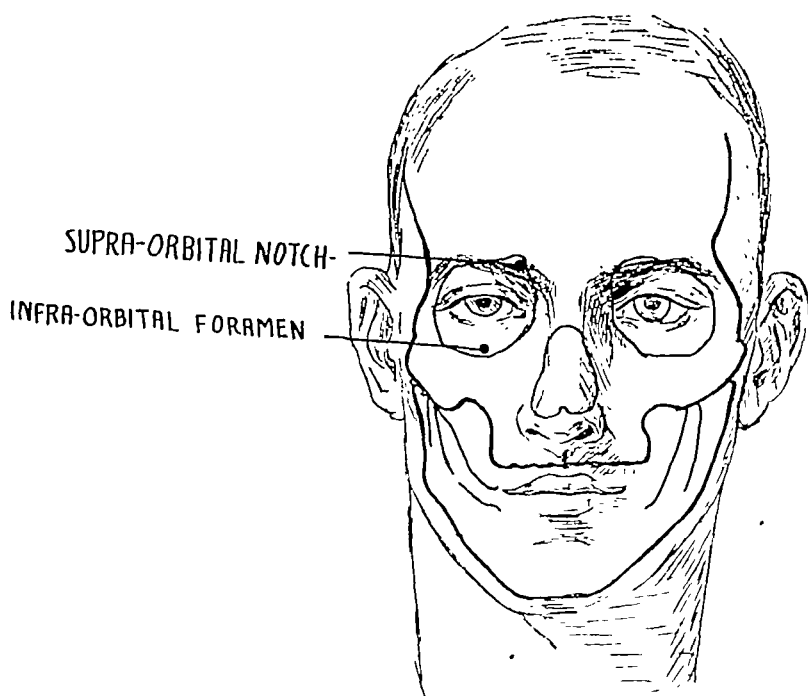


Fig. 111.—Points of injecting the supra-orbital and infra-orbital nerves.

orbital notch is marked by the index fingernail of the left hand pressed upon it while a small flexible needle is slipped along the fingernail down into the notch, just below the eyebrow, at a distance of about 1 inch from the middle. As the point of the needle hits the bone, the patient will experience a sharp pain up to the top of the head. This is the sign that the needle is in the correct position. Now 2 or 3 drops of 2 per cent novocain solution are injected, and the sensation

of the forehead is tested by a pinpoint. If anesthesia in this area has resulted, the syringe with novocain is replaced by one with 95 per cent alcohol and about 10 drops are injected slowly, 1 drop at a time. There should result anesthesia of the forehead and top of the head up to the midline, except

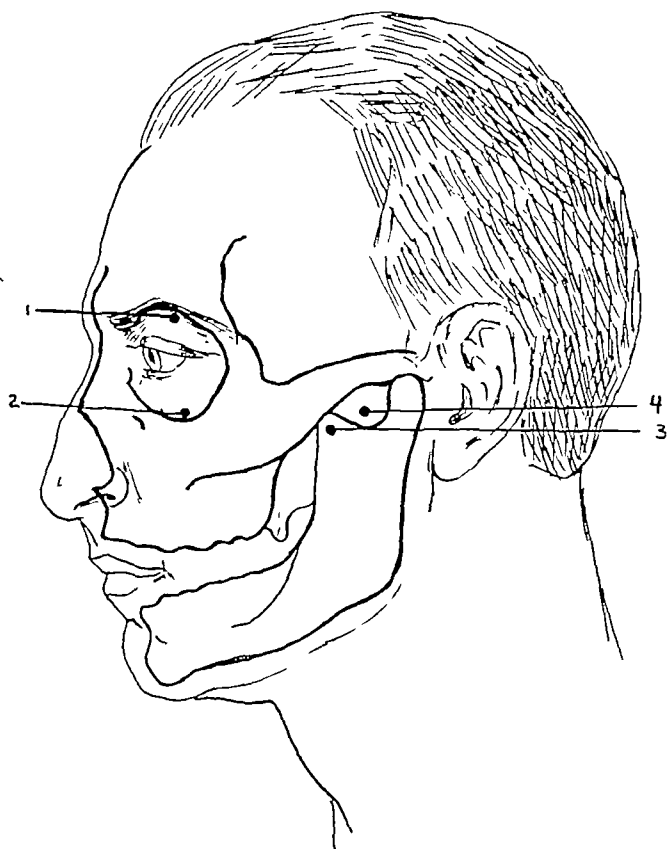


Fig. 112.—Points of injection of supra-orbital, infra-orbital, maxillary and mandibular nerves. 1, Supra-orbital notch; 2, infra-orbital foramen; 3, coronoid process of mandible; 4, notch of mandible.

the central triangle of the skin between the eyebrow and midline which is spared, because it is supplied by the supra-trochlear nerve.

**Neuralgia of the Second Division.**—(a) *Technic of Injection of the Infra-orbital Nerve.*—(Figs. 113, 111, 112.)

The infra-orbital foramen lies about 1 inch from the midline. A long needle is inserted at a point about one-fourth of an inch outside and above the angle of the ala nasi, the insertion being made down to the bone in an upward and slightly outward direction. It is important to keep the left forefinger firmly pressed against the rim of the lower margin of the orbit, to insure that the needle does not slip over the orbital margin and so penetrate the orbit, where serious damage might be done. The patient will complain of pain in the nose and

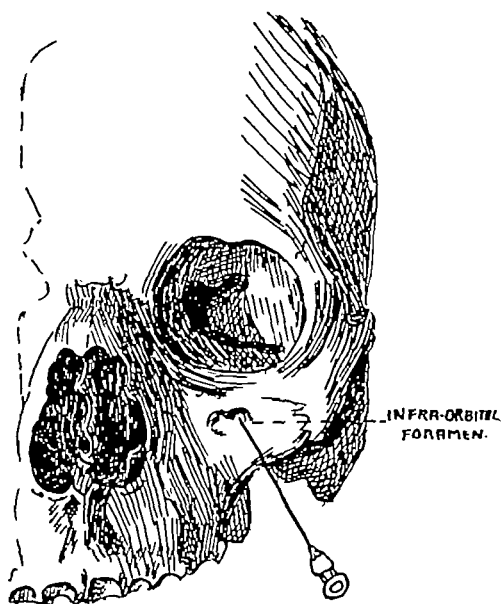


Fig. 113.—Anatomical view showing injection of infra-orbital nerve.

upper lip as soon as the needle strikes the nerve. Three or 4 drops of 2 per cent novocain solution are then injected, which will be followed by anesthesia of the upper lip, lower eyelid, cheek, and side of nose. Then 1 cc. of 95 per cent alcohol is slowly injected, a dressing being held firmly pressed against the cheek close to the needle to prevent swelling.

(b) *Technic of Injection of Second Division at Foramen Rotundum.*—(Figs. 114, 115, 112.) Injection of the second and third divisions at the foramen rotundum and foramen

ovale, respectively, and gasserian ganglion should be attempted only by the skilled physician. A skull with mandible in place always should be before the operator for guidance by landmarks during injection of the second or third division. For injection of the second division it is well beforehand to mark off on the needle  $4\frac{1}{2}$  to 5 cm. from the point upward. The method of approach to the foramen rotundum and foramen ovale is through the outside of the cheek.

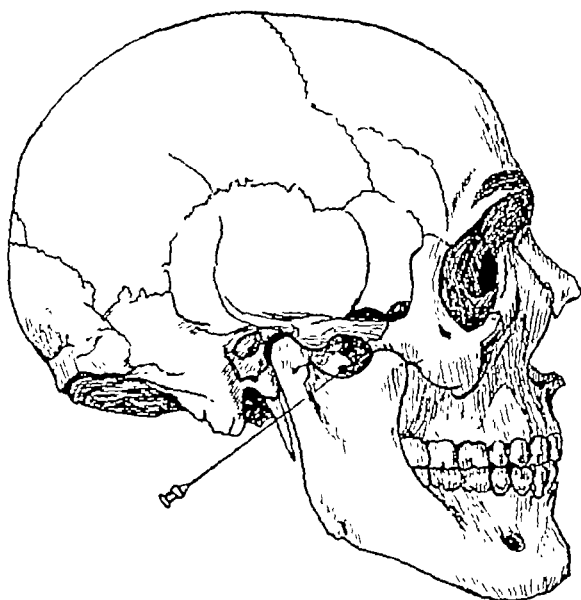


Fig. 114.—Lateral view of skull showing anatomical landmarks for injecting the second and third divisions.

First feel the coronoid process of the mandible, then insert a long, flexible needle behind this process. Now direct the needle slightly forward at an angle of from 15 to 30 degrees, and upward at an angle of about 15 degrees.

The object is to hit the external pterygoid plate (Fig. 116), and then to manipulate the needle forward until its point is felt to slip in front of the anterior edge of the plate, where the nerve will be found at a slightly greater depth. If the nerve is not found on the first attempt the needle must be



partially withdrawn and its angle of direction altered slightly upward or downward, until the nerve is found. At a depth of 5 cm. the needle should be in the foramen rotundum. The penetration of the nerve by the needle will be indicated by pain in the distribution of the second division in the upper jaw, teeth and gums. The injection first by novocain and then by alcohol is made as for the third division injection. (See below.)

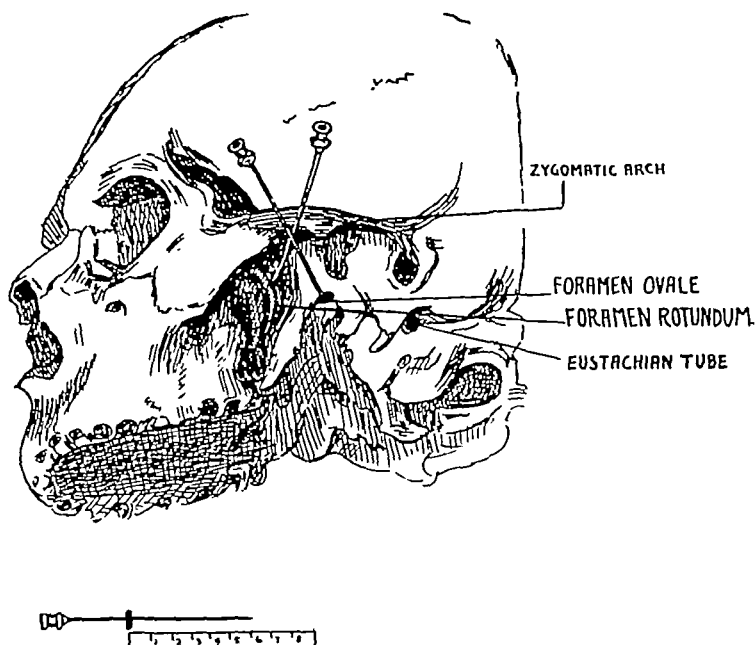


Fig. 115.—Anatomical view showing the foramen rotundum and foramen ovale at sites for injection of the second and third divisions respectively. Piece of rubber marks the length of needle to be inserted down to the nerve.

**Neuralgia of the Third Division.**—(a) Peripheral injection of this division is made in the mental foramen, through the cheek or into the inferior dental nerve on the inner side of the ramus of the lower jaw. (Figs. 116, 117.)

(b) *Injection of Third Division at Foramen Ovale.*—(Figs. 114, 116, 115, 112.) A long flexible needle is inserted in the middle of the zygomatic arch, through the sigmoid notch of the mandible, about 1 inch forward from the middle of the

external auditory meatus. Push the needle inward pointing it slightly upward and backward. Pain referred to the ear indicates that the eustachian tube has been touched because the needle is too far backward. Withdraw it a little and push it further forward. Pain felt in the throat and back of the tongue means that the needle has been pushed too far. By the method of trial and error the third division can even-

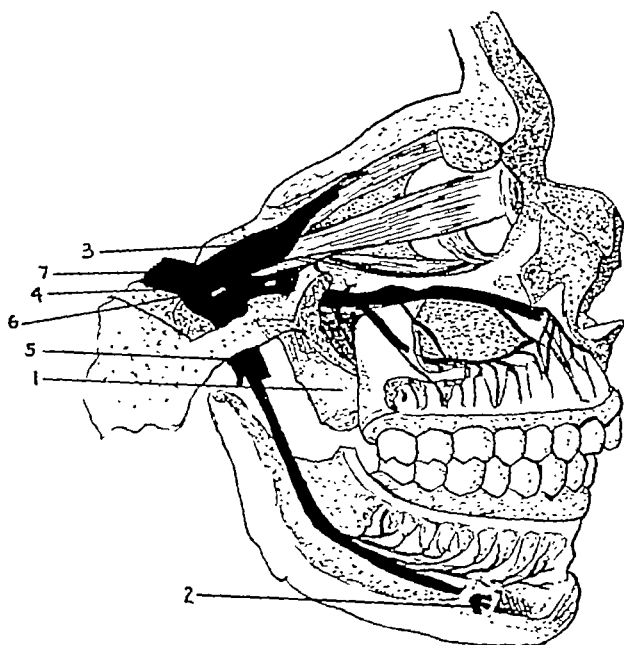


Fig. 116.—Anatomy of trigeminal nerve. 1, External pterygoid process of sphenoid bone; 2, mental foramen; 3, ophthalmic division; 4, maxillary division; 5, mandibular division; 6, gasserian ganglion; 7, sensory root of gasserian ganglion.

tually be found. As soon as the needle strikes the nerve, the patient complains of pain in the lower lip, chin, or tongue. Inject 2 or 3 drops of 2 per cent novocain and test these parts for anesthesia. When this appears change the syringe to 95 per cent alcohol and inject slowly a drop at a time. As the alcohol is injected, a burning sensation is felt in the lower lip, cheek and chin, and a wooden feeling spreads along the

lower jaw and in front of the ear. The burning sensation soon passes off whereupon more alcohol is injected, 2 or 3 drops at a time, until the anesthesia is complete and no more burning is experienced. The pain then ceases at once.

If the burning pain spreads to the nose, cheek, and eye, and anesthesia appears over the upper two divisions of the nerve, this indicates that the gasserian ganglion has also been injected.

Successful injection results in anesthesia to pain and touch on the side of the lower lip, inside of cheek, lower jaw, teeth, gums, and tongue, on a strip of skin extending from the lower

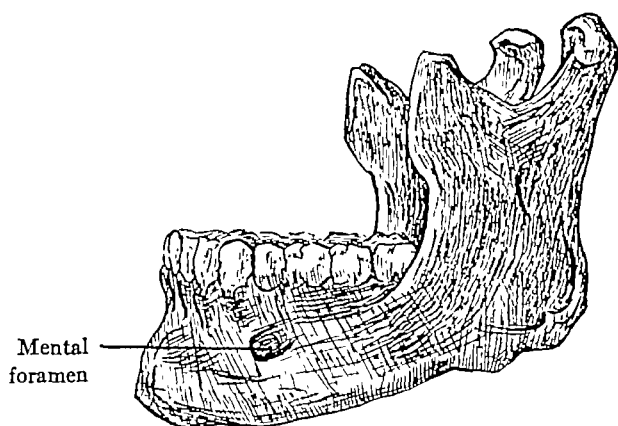
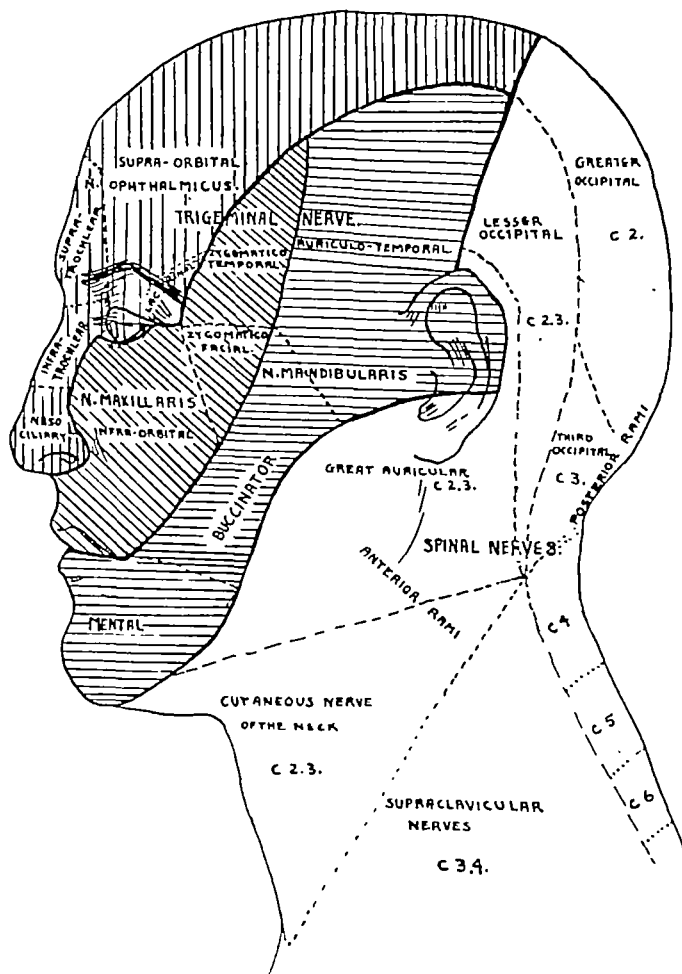


Fig. 117.—Mandible showing mental foramen.

angle of the mouth toward the temple, and in the external auditory meatus and tympanum (Fig. 118). There will also be paralysis of the masseter, temporal and pterygoid muscles, so that the lower jaw when opened widely will be pushed toward the side injected.

Following an injection the patient may complain of deafness and intense vertigo and he may vomit and have facial paralysis and coarse nystagmus due to leakage of the alcohol toward the cerebellopontine angle. This can be prevented by making the injection very slowly.

The chief danger, arising from the unintentional injection of the gasserian ganglion, is corneal ulceration. This can be



- OPTHALMIC DIVISION.  
 ▨ MAXILLARY DIVISION.  
 ▨ MANDIBULAR DIVISION.

FIG. 118.—Sensory area of head showing the three divisions of the fifth nerve.

recognized early by the steamy ground-glass appearance of the cornea, with circumcorneal injection. If this is observed, a drop or two of atropine in the eye with closure of the lids

by a firm bandage for twenty-four hours may prevent further ulceration. Whenever the corneal reflex is abolished after an injection of the foramen ovale, the eye requires special attention, by shielding it with an eye shield or crystal and irrigating with 2 per cent boric acid lotions and instillation of 10 per cent argyrol.

Avulsion of the sensory root of the gasserian ganglion, also referred to as subtotal resection of the root, or retrogasserian neurectomy, offers the only permanent relief from trigeminal neuralgia. In this operation the sensory root fibers (Fig. 116) of the second and third divisions are destroyed never to regenerate functionally. The ophthalmic division and the motor root of the fifth nerve are left intact whenever possible to avoid the risk of keratitis and paralysis of the jaw. Nearly the entire operation can be done under local anesthesia in the sitting position, via the subtemporal route. Sufferers from trifacial neuralgia who also have cardiac decompensation and auricular flutter require preliminary digitalization, otherwise the operation may be a success but the patient will succumb to cardiac failure.

The surgical risk from this operation is small indeed, but the greatest danger is ulcer of the cornea which may so resist all treatment that enucleation may have to be done. The patient should be informed of this danger beforehand. Usually, however, this hazard will not deter him from submitting to surgery, in his desperate search for relief from pain.

#### RELIEF OF GLOSSOPHARYNGEAL NEURALGIA

The relief of pain from glossopharyngeal neuralgia is required infrequently, as this type of neuralgia is uncommon. It is not to be confused with trigeminal or superior laryngeal neuralgia.

After all causes of pain in the throat, such as organic diseases of the pharynx, neck, posterior cranial fossa, etc., have been eliminated one is justified in considering the pain due to glossopharyngeal neuralgia and in instituting treatment for this condition.

There are three methods of treatment for the relief of this type of neuralgia: Alcohol injection of the nerve near the jugular foramen, neurectomy of the ninth nerve as high up in the neck as possible, and intracerebral section of this nerve.

Alcohol injection in the region of the jugular foramen is not to be attempted by the inexperienced, as the danger of paralysis of the bulb is great. For the injection the needle is inserted in front of the tip of the mastoid, from where it is passed inward and slightly upward to a depth of  $1\frac{1}{2}$  inches. When the needle strikes the nerve, pain will be felt in the lateral region of the throat radiating to the eustachian tube and behind the ear.

Injection is then made with 2 per cent novocain followed by 95 per cent alcohol, described under trigeminal neuralgia, with resulting relief of pain in, and anesthesia of, the pharynx, and loss of taste on the posterior third of the tongue.

This method and neurectomy of the ninth nerve may afford relief varying from six months to two years, after which the pain recurs. Intracerebral section of the glossopharyngeal nerve effects a permanent cure from the pain.

#### RELIEF OF SUPERIOR LARYNGEAL NEURALGIA

Superior laryngeal neuralgia is even more uncommon than the glossopharyngeal type, from which it must be differentiated. The former must not be mistaken for tuberculous or malignant disease of the larynx and epiglottis, or for the gastric crises of tabes.

In alcohol injection for the relief of pain from this form of neuralgia, only the internal branch of the superior laryngeal nerve is injected. With the left index finger on the greater cornu of the hyoid bone (Fig. 119), the needle is inserted in the midline between the superior laryngeal margin and the hyoid bone and is carried laterally through the thyrohyoid ligament, which offers considerable resistance toward the cornu of the hyoid bone. The internal branch is then located by probing with the needle until pain is felt in the side of the neck shooting up to the ear, and from the side of the

thyroid cartilage darting up to the angle of the jaw. Successful injection with novocain and alcohol produces anesthesia

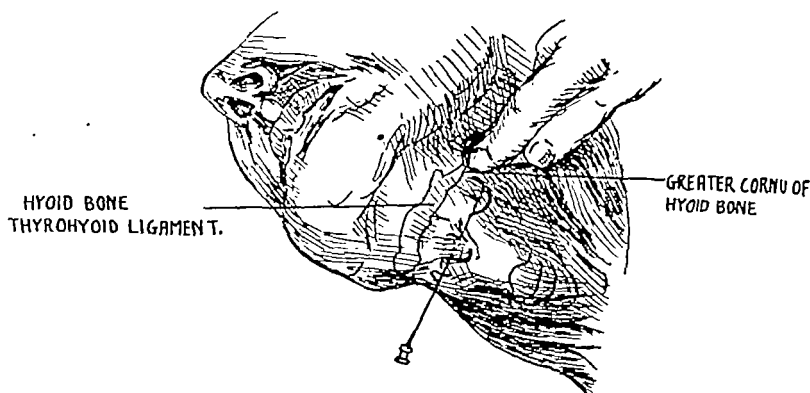


Fig. 119.—Injecting the superior laryngeal nerve.

of the larynx and epiglottis, and relief from pain. Neurectomy of the internal branch gives the same results as alcohol injection.

#### RELIEF OF OCCIPITAL NEURALGIA

Occipital neuralgia is not common. When severe pain is experienced in back of the neck radiating over the occiput into the parietal region associated with hyperesthesia of the scalp, neuralgia of the great occipital nerve may be the cause, but rheumatic myositis of the neck muscles, arthritis deformans, caries or tumors of the first or second cervical vertebra and hysteria must be ruled out.

The pain of occipital neuralgia will usually be relieved by external heat and counterirritants, as mustard plaster, to the occipital region, or alcohol injection into the great occipital nerve.

For alcohol injection, the needle is inserted vertically downward to the bone at the point of emergence of the nerve midway between the mastoid process and the first cervical vertebra, and about  $\frac{1}{2}$  inch below the level of the occipital protuberance. Subsequently there will be anesthesia of the scalp in the occipital region and relief from pain in that region.

## RELIEF OF PAIN FROM SLUDER'S NEURALGIA

Relief of pain from Sluder's neuralgia may be obtained by extirpation or cocainization of the sphenopalatine ganglion.

The treatment of this form of neuralgia is most efficiently performed by the nose specialist and the reader is referred to the literature on rhinology for further information on this subject.





## CLINIC OF DR. ROBERT O. RITTER

### ST. LUKE'S HOSPITAL

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#### RELIEF OF LUMBAGO AND SCIATICA

IN adult life there is no more common complaint than backache with or without sciatic radiation. The majority of patients with backache have, without a thorough examination, been treated for lumbago or sciatica. These two complaints and the disabilities resulting from them are serious problems which confront the general practitioner, the orthopedic and the industrial surgeon. Any patient seeking treatment for backache or sciatic pains requires a complete and thorough history and physical and x-ray examination. Such an examination and history will, in most cases, lead to the discovery of the causative pathology. Only then can rational therapy be instituted.

There are many anatomic variations in the lower spine which may at times produce pain and disability. Among these are sacralized fifth lumbar transverse processes (Fig. 120), spina bifida occulta, abnormal articulations, an abnormally oblique lumbosacral angle, spondylolisthesis (Figs. 121, 122), pronounced hollow back and static factors. Flat feet and short Achilles tendons produce fatigue of the lumbar muscles, and often a severe back strain. Poor sitting posture in a chair or in an automobile during a long drive often causes backache.

Genito-urinary, gynecological and neurological conditions should be investigated and eliminated. Pains in the lumbosacral region and over the sacrum should make one think of disease of the prostate and seminal vesicles. In women static backache often cannot be distinguished from that due to pelvic disorders. The gynecologist should be consulted in all ques-



Fig. 120.

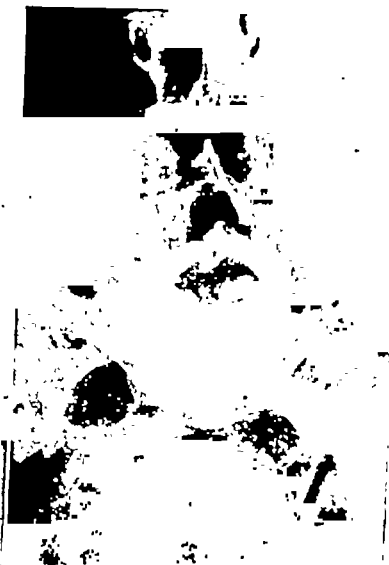


Fig. 121.

Fig. 120.—Mrs. B. I. Sacralized fifth lumbar transverse process. x-Ray showing tibial grafts in place.

Fig. 121.—x-Ray of A. S., showing fifth lumbar vertebra slipped forward into the pelvis.



Fig. 122 —Complete fifth lumbar spondylolisthesis. Two large tibial grafts were inserted across the lumbosacral joint

tionable cases. A careful examination will eliminate many radical intrapelvic operations. However, it has been our experience that uterine trouble is more often ruled out than not.

Pain in the back is present in certain diseases of the nervous system. Tabes, cord tumors, disease of the cord itself, and peripheral nerve disturbances are to be ruled out. During the last year four patients, one man and three women, entered our clinic because of severe pain in the low back. Or-



Fig. 123.

Fig. 124.

Fig 123—J. P. Sciatic scoliosis with arthritis. Not relieved by palliative measures.

Fig. 124—J. P. After trisacral fusion. No return of symptoms after four years.

thopedic and x-ray examinations failed to explain fully the cause for all the complaints. A thorough neurological examination revealed a multiple sclerosis in each case.

Metastatic disease of the spine and pelvic bones causes extreme pain. Pain due to malignancy is not relieved by rest on a rigid bed or by other therapeutic measures as is the pain from any other cause.

There can be no doubt that backache and sciatic pains are very often due to the presence of an actual osteo-arthritis

of toxic or infectious origin. (Figs. 123, 124.) They may also be due to age and to certain back-straining occupations.

When an inflammatory process is added to a mechanically unstable joint, pain and disability follow. The pain may come on suddenly or insidiously, and may radiate down one or both sciatic nerves, the gluteal nerves or down the front or sides of the thighs. It may be so severe as to be immediately disabling, as in sudden twists of the body or when a heavy object is lifted. In many instances where there has been an injury, the pain does not appear until a day or two later. The reason for this very common occurrence has not been fully explained. By some it is considered a ligamentous strain followed by edematous changes or a tear of muscle fibers with resulting spasm. By others it is regarded as a myofascitis of a rheumatic nature. If the  $x$ -ray shows arthritic changes they are due either to disease or long continued strain or both.

Many cases of disease and strain of the sacro-iliac joints occur but the lumbosacral is more often the site of the lesion. In some cases it is difficult or impossible to determine in which of these joints the trouble exists. However, a careful physical and  $x$ -ray examination will usually lead to a good working diagnosis.

Pain along the course of the sciatic nerve occurs in both sacro-iliac and lumbosacral lesions. If it is unilateral, either may be involved. If bilateral, the lesion is usually in the lumbosacral joint. Gaenslen's sign for sacro-iliac lesions is very reliable. "Hyperextension of one hip with the opposite knee and hip acutely flexed to fix the lumbar spine, including the lumbosacral joint. Pain is present only in the sacro-iliacs, ruling out lumbosacral cases."

The etiology of any given case will govern the treatment. This may be either conservative or operative.

All acute painful cases with or without radiating pains should be put at rest on a rigid bed, and some form of physical therapy, such as heat and massage, begun. Large doses of salicylates are beneficial. Head and pelvic traction or a plaster cast may be necessary to relieve muscle spasm in a

certain number of cases. All foci of infection should be carefully sought and removed. This is especially true in the intestinal tract, teeth and tonsils. However, teeth should not be extracted just because they are devitalized. (Fig. 125.)

In cases of low backache, where mild static faults are present, the skeletal alignment is corrected with supporting corsets or braces. Graduated exercises, massage and physical therapy are of value. In sacro-iliac strains without extreme



Fig. 125.

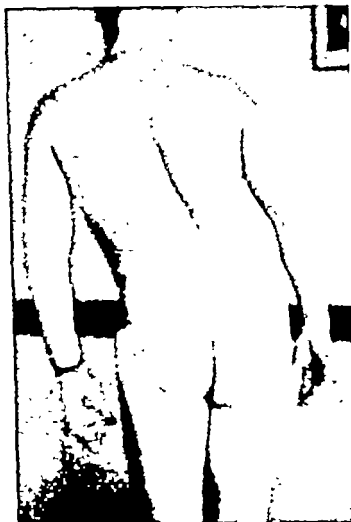


Fig. 126.

Fig 125.—J. C. Sciatic scoliosis. Relieved by clearing up infected teeth and gums, and palliative measures.

Fig 126 —S. K L. Scoliosis. Severe lumbago. Relieved by palliative measures.

pain or muscle spasm, a firm adhesive plaster strapping gives immediate relief. The one disadvantage of adhesive is that some skins are easily irritated by it. For this reason a well fitting, non-elastic corset is preferable. In a great many cases of painful sacro-iliacs an ordinary belt such as men wear, buckled tightly around the pelvis just above the trochanters, gives prompt relief. (Fig. 126.)

In some cases where the disability comes on suddenly following an injury, manipulation under complete anesthesia and

rest on a rigid bed for a few days are sufficient. Other more severe cases require immobilization with a cast or brace.

In the many cases not relieved by conservative measures, surgery becomes necessary. These are the chronic cases in which there is definite x-ray evidence of disease or deformity. In a certain number of cases, affection of the lumbosacral or sacro-iliacs cannot be differentiated. In these, all three joints should be ankylosed. For the lumbosacral arthrodesis the Hibbs technic has been quite generally used with the addition of two large tibial grafts. These grafts are cut from the flat surface of the tibia. One end of each is cut on an angle that just fits the lumbosacral angle. The grafts are fitted in edgewise, one on either side of the denuded spinous processes, with the medullary surfaces together. In all cases where this type of graft has been used, a very heavy mass of bone has been formed, and no failure of ankylosis has occurred. Such has not always been true where pieces of ilium were used.

The Smith-Petersen operation is adaptable to one or both sacro-iliacs, but not to the combined or triple arthrodesis. For the triple arthrodesis the extra-articular operation on the sacro-iliacs is the method of choice.

Operation is certainly advisable if the disability is a real handicap, especially in a wage earner. The operation is as safe as any major surgery, but it has a disadvantage in that it requires eight to twelve weeks for a solid ankylosis to take place.

When the excellent results from operative, as compared to nonoperative, treatment are compared, we feel that surgery is more conservative and time saving for the patient than mechanical treatment.

## CLINIC OF DR. LOUIS T. CURRY

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#### TREATMENT OF EARACHE

EARACHE (otodynia, otalgia) is caused by pathology in the middle ear, the external ear or the internal ear, or is referred from neighboring structures in the mouth, pharynx, larynx or nose. Earache is characterized clinically by pain in the ear region and pathologically by stimulation of the complicated sensory nerves of the ear mechanism.

As a foundation for this discussion, I shall first briefly summarize the sensory innervation of the ear mechanism, as taken from the anatomies of Cunningham and Spalteholz, and then proceed with a consideration of earache, its differential diagnosis and treatment.

##### *Sensory innervation of the ear mechanism:*

##### 1 In the ear itself.

##### (A) External ear.

##### 1. Auricle.

##### (a) External surface.

- (1) Auriculotemporal nerve, from mandibular branch of fifth nerve, supplies upper half.
- (2) Great auricular nerve, from C-2 to C-3 of cervical plexus, supplies lower half.

##### (b) Cranial surface.

- (1) Lesser occipital nerve, from C-2 to C-3, supplies upper half.
- (2) Great auricular nerve, from C-2 to C-3, supplies lower half.

##### 2 Scalp behind ear—lesser occipital and great auricular nerves.

##### 3 Zygomatic region—auriculotemporal nerve from mandibular fifth.

##### 4 Internal auditory canal and drum membrane.

- (a) Auriculotemporal nerve from mandibular division fifth



supplies external auditory canal and external surface of the ear drum.

- (b) Auricular branch from close below ganglion jugulare of vagus (Arnold's nerve) supplies concave surface of auricula and external acoustic meatus, and communicates with glossopharyngeal nerve.

(B) Middle ear.

1. Tympanic plexus supplies mucous membrane of tympanum and mastoid cells. Tympanic plexus is formed by tympanic nerve (from petrous ganglion of glossopharyngeus nerve) which enters the tympanum where it is joined by carotico-tympanic branches from the carotid sympathetic plexus on the internal carotid artery and a twig from the genicular ganglion of the facial nerve.

(C) Inner ear.

1. Supplied by two divisions of the specialized auditory nerve—cochlear and vestibular.

II. Neighboring structures.

- (A) Otic ganglion: Fibers of tympanic branch of glossopharyngeal nerve reunite with small nerve from genicular ganglion of facial nerve (ramus anastomaticus cum plexus tympanico) to form the lesser superficial petrosal nerve. This nerve eventually ends in the otic ganglion on the trigeminus nerve.

- (B) Sphenopalatine ganglion: Greater superficial petrosal nerve (mostly sensory fibers) from genicular ganglion of facial nerve unites with deep petrosal nerve from sympathetic on internal carotid artery to form nerve of pterygoid canal (O. T. vidian nerve). It passes through sphenopalatine ganglion and supplies mucous membrane of soft palate.

- (C) Pharyngeal plexus: Pharyngeal branches of glossopharyngeal nerve supply mucous membrane of pharynx. These combine with pharyngeal branches from ganglion nodosum of the vagus nerve and the superior cervical ganglion of the sympathetic to form the pharyngeal plexus.

(D) Tongue and tonsils:

1. Lingual nerve from mandibular branch of fifth nerve supplies the anterior two thirds of the tongue, the mucous membrane of the side wall and the floor of the mouth. The chorda tympani from the facial nerve is carried in the lingual nerve.
2. Terminal branches of the small glossopharyngeal nerve supply the posterior third of the tongue and the tonsils.
3. Vagus nerve sends fibers to the base of the tongue

(E) Larynx and epiglottis.

1. Glossopharyngeal nerve supplies anterior surface of epiglottis.
2. Superior laryngeal nerve (internal branch from vagus) supplies mucous membrane of larynx and passes upward to epiglottis and base of the tongue.

From this sketchy summary of the complex ear innervation one concludes that earache may arise from stimulation of C-2 and C-3 of the cervical plexus and cranial nerves V, VII, VIII, IX and X.

*Earache: Its differential diagnosis and treatment.*

I. Aural pain from disease in the ear mechanism.

(A) Middle ear disease causing pain.

- (1) Acute catarrhal otitis media.
- (2) Acute serous otitis media.
- (3) Acute suppurative otitis media.
- (4) Acute mastoiditis.
- (5) Chronic suppurative otitis media and chronic mastoiditis.
- (6) Chronic adhesive middle ear catarrh.
- (7) Blue ear drum.

1. **Acute Catarrhal Otitis Media.**—As a rule acute catarrhal otitis media is a complication of acute coryza. The patient notices a fulness in the ear which may later become severe. There may be crackling and buzzing noises in the affected ear. The ear drum usually shows some congestion of the blood vessels especially over the handle of the malleus. There is usually some diminution of hearing. The treatment consists in the treatment of the cause.

2. **Acute Serous Otitis Media.**—Acute serous otitis media arises when acute catarrhal otitis media progresses with the formation of serum in the tympanum. If the tympanum fills, the ear drum appears unusually clear, although the patient complains of fulness in the ear and the hearing is impaired. If the serum partially fills the tympanum, its upper edge may be seen as a hair line shining through the drum head. The pain is in the ear and usually disappears in a day or two. Treat the underlying cause. Four or 5 drops of warm 5 per cent carboglycerin may be instilled in the aching ear every two or three hours for relief of the pain. Application of heat is usually comforting. Hot dressings, hot water bag, electric pad or the incandescent light may be used. If the serum is not absorbed in a few days, it is advisable to perform a myringotomy with careful antiseptic precautions. The serum is then blown out of the tympanum by inflation through the

eustachian tube. Inflations may be done in three ways: (1) Valsalva method—patient holds his nostrils, closes his mouth and employs forcible extirpation; (2) Politzer bag—blast of air is shot into one nostril while closing the other at the time patient is asked to say K or swallow a sip of water; (3) eustachian catheter—catheter passed through nose below inferior turbinate and inserted into eustachian opening. Through catheter blast of air is applied, blowing secretion from tympanum. Auscultation tube from affected ear to ear of operator is necessary to hear when this is accomplished.

3. **Acute Suppurative Otitis Media.**—Acute suppurative otitis media is the most frequent cause of earache. Actually this condition is severe, acute, advanced catarrhal otitis media. Therefore, it usually follows head colds or one of the exanthemata. The pain is severe and is felt in the ear. It is usually continuous but may have exacerbations. It is usually worse at night. The pain is relieved, as a rule, if the ear drum ruptures or if a paracentesis is done. With severe infections, the earache may continue for several days even after drainage has been given. The discharge may be serous to purulent with any degree of intermixture. It may be slight or profuse. Before rupture or opening of the ear drum, the drum head may be generally red to very red and bulging. Blood vesicles may cover the ear drum and fill a large portion of the external auditory canal. There is usually an elevation of temperature and a decided defect in the hearing.

*Treatment.*—1. External heat applied to the ear is the best method of relieving the earache. This may be applied by means of a hot water bag, moist hot dressings or an electric pad. Opium for relief of earache is contraindicated because it may mask the progress of the disease.

2. Ear drops for relief of pain are prescribed by many otologists. The favored prescription is phenol and glycerin (1:20). This mixture is to be used warm in the aching ear every two or three hours (3–5 drops).

3. *Myringotomy.*—The ear drum must be opened as soon as any bulging of the drum membrane is seen, or sooner if

the earache continues for twenty-four hours or longer, even in the absence of bulging. Mastoiditis and intracranial complications occur less frequently where early paracentesis is done. Paracentesis of the ear drum is carried out, using proper antiseptic precautions, with an anesthetic, either local or general.

*Local Anesthetic.*—Equal parts of phenol, menthol and cocaine hydrochloride are used. This thin paste is applied sparingly with a small cotton applicator to the bulging area of the ear drum. It is well to warn the patient that the first touch hurts. The swab is held in place as long as the patient can bear it, which is usually a few seconds. The same procedure is continued until the applicator can contact the inflamed ear drum without much discomfort for a minute or two. The incision is then made through the bulging area of the ear drum, which should appear white if properly anesthetized with a light paracentesis knife. If there is no bulging, the incision is made in the posterior quadrant of the ear drum. In certain types of influenza ears, the ear drum cannot be seen because of blebs. These can be opened only by guess. With gentleness and care, an experienced surgeon can insert the knife through the blebs and toward the ear drum until the point of the knife gently strikes the promontory without harm. I have found no need for extensive incision of the ear drum. If the tympanum continues to fill with pus, the small incision enlarges with the infection. If drainage is slight, the small or large incision closes quickly and another opening may be required.

*General Anesthetic.*—Nitrous oxide or ethylene are ideal anesthetics for myringotomy. The advantages are evident, but there are drawbacks. The cost is greater for a general anesthetic, since more time is required of the physician, an anesthetist's services are required, and there is a hospital bill. Another handicap to the general anesthetic is that the indications for paracentesis often arise during the acute exanthemata while the patient is quarantined.

*Without Anesthesia.*—Myringotomy may be performed without anesthesia, but the operation causes severe pain.

Earache may disappear after drainage has been given, to reappear if any blockage takes place. This can be remedied by instilling a few drops of hydrogen peroxide into the meatus. Thus drainage is reestablished. When earache continues after paracentesis, external heat is applied.

The draining ear should not be plugged with cotton. The external canal must be kept clean by dry wicks, frequently changed, or by frequent wiping of the external meatus. When the discharge is very thick, it may be cleaned out by gentle syringing with warm boric or soda water. At night, the ear toilet is best cared for by layers of gauze over the pinna which are held in place by a hair net tied under the chin. The cavum conchae and incisura intertragica must be kept clean with warm saline solution bathing daily and covered with a thick layer of zinc oxide ointment. If this is not done, the patient often develops a painful dermatitis from the irritating discharge.

**4. Acute Mastoiditis.**—Acute mastoiditis is usually a complication of acute suppurative otitis media. Pain over the mastoid, often present when myringotomy is done, usually disappears after drainage is instituted. Pain over the mastoid, significant of acute mastoiditis, usually starts after the ear has been draining for two or three weeks. It may, however, be present in the beginning of the otitis media and persist until relieved by surgical intervention. In other cases, it may appear after the ear discharge has ceased. There may be changes in the soft parts over the mastoid process and tenderness to pressure, especially over the antrum, the tip or the emissary vein. In adults there may be no tenderness when pressure is applied over the mastoid or alterations in the soft structures even in the presence of an acute mastoiditis.

Mastoid pain is usually worse at night. If the patient with an acute otitis media has pain at night in the mastoid area and a discharge which is becoming more purulent, formation of a mastoid abscess is indicated. Pain may also be

caused by subperiosteal abscess or Bezold's abscess. The pain is less after the abscess forms than during its formation. Tenderness over the abscess is noted upon palpation. The subperiosteal abscess may form posterior, superior or anterior to the auricle. A Bezold abscess is caused by a rupture of a mastoid abscess through its tip. These may appear superior, in or below the sternocleidomastoid muscle. Occasionally they appear posterior or anterior to this muscle.

*Treatment.*—Early mastoid pain is treated by hot applications as previously described. Some otologists prefer ice packs or ice coils, feeling that an abscess is more often avoided. The cold aids in control of the pain.

The indications for operative interference in acute mastoiditis differ for the small child and for the adult.

In a small child operative interference is indicated:

1. When subperiosteal abscess develops if the ear has previously had proper treatment and drainage.
2. If symptoms of threatened intracranial complications appear, as meningismus, meningitis, lateral sinus thrombosis, brain or cerebellar abscess.

In an older child or in an adult the indications for operation are:

1. As above.
2. As above.
3. If earache continues for seven to ten days after proper treatment has been instituted.
4. If the discharge continues to be purulent after proper treatment and shows no evidence of diminishing for four weeks.
5. If the patient continues to have rather high fever and palpable changes over the mastoid for two weeks, even though proper treatment has been given.

The operation indicated is a simple mastoidectomy which has for its object the drainage of the mastoid abscess. Usually in adults the external wall of the antrum is opened, although the antrum is not necessarily the location of the abscess. In

infants, since mastoid cells have not developed, the operation is more properly called an antrotomy.

**Recurrent Mastoiditis.**—This term is applied to patients who have had simple mastoidectomies and develop acute suppurative otitis media. The pus backs up into the antrum which is immediately below the soft parts behind the auricle. An abscess may develop in this region which causes the pain typical of any abscess. After using heat, if the abscess does not subside, it is opened and drained as any other abscess, after which the symptoms of otitis media usually promptly subside if the previous mastoidectomy has been complete. Occasionally it is better to expose the mastoid cells area and seek for further infected broken-down cells which should be eradicated.

**Gradenigo Syndrome.**—This properly comes under the heading of mastoiditis. Severe headache referred to the side of the head in the region of the affected ear, purulent otitis media and paralysis of the sixth cranial nerve on the same side are the cardinal symptoms of this syndrome.

**Treatment:** Most otologists agree that at least a simple mastoidectomy is indicated when symptoms of this syndrome are present. Others insist upon drainage of the petrous tip cells, which is a difficult and dangerous procedure. Swelling of the gasserian ganglion which causes the sixth nerve to be put on a stretch is one of the theories given for paralysis of this nerve. In these conditions I favor conservative treatment as taught me by Dr. George E. Shambaugh. We used conservative treatment on a woman with chronic suppurative otitis media accompanied by Gradenigo's syndrome five years ago. She recovered and has been free from recurrence since. I have treated twenty patients successfully by conservative treatment, *i.e.*, simple mastoidectomy and keeping the wound open until dry. One of my patients died. His pain continued in the side of the head after the mastoid operation. Drainage continued for one month, after which the pain subsided and the drainage ceased. He moved to another city, had a recurrence of headache, was operated and died.

I do not know the nature of the operation performed. Recently I treated a boy with typical symptoms of this syndrome, but his otitis media was mild. His aural discharge stopped, his headache subsided and his lateral rectus paralysis disappeared in two weeks. I decided not to operate upon his mastoid. His ear is now dry, his drum membrane healed and he is free from headache but his lateral rectus paralysis has reappeared. He has been under observation for three weeks since his ear drum became normal. The outcome is to be awaited.

5. **Chronic suppurative otitis media and chronic mastoiditis** are not as important from the standpoint of earache as they are from absence of earache and danger of intracranial complications. Chronic suppurative otitis media may be discussed under two very different types:

1. Inflammatory changes limited to mucous membrane of the middle ear chambers. This is misnamed the "nondangerous type," but should be called the less dangerous type.

2. Changes in the middle ear associated with a bone-invading process. This is properly called the dangerous type.

In the first type, pain is rarely a symptom if the ear is kept clean and properly treated. Occasionally a polyp forms which blocks drainage and causes earache. The treatment is to remove the polyp with an ear snare or cautery and reestablish proper drainage. Silver nitrate in solution or fused on a probe, or chromic acid fused on a probe may be used to cauterize. In using the chromic acid bead, the bead should be cherry red and not black in color to cauterize properly.

Individuals with chronic otitis media sometimes develop an acute otitis media in the same ear which gives the otalgia of that disease. The treatment is practically the same except that operative interference may be indicated earlier because of the greater damage of intracranial complications.

In the second type of chronic suppurative otitis media, earache is more common but seldom severe. It consists usually of a dull ache in the ear or is referred to the side of the head as a heavy feeling. Occasionally the pain may be deep



seated or boring in character. Its significance is quite important, since it may indicate a threatened intracranial invasion. In this type of ear disease we deal with sequestration, caries and cholesteatoma. Usually the treatment leads to radical operative treatment, unless the hearing in the opposite ear is more seriously affected. The radical mastoid operation is practically never done because of pain. Therefore, a description of it is not in order here.

The complications of chronic suppurative otitis media should be mentioned, but earache is not a prominent sign in any of them. They may intervene without any sign of earache or there may be a warning sign of a heavy feeling in the side of the head. Very rarely is there any severe pain.

#### INTRACRANIAL COMPLICATIONS OF CHRONIC SUPPURATIVE OTITIS MEDIA

1. Labyrinthitis, which may be circumscribed or diffuse and serous or suppurative.

2. Lateral sinus thrombosis.

3. Meningitis, which may be serous or suppurative and circumscribed or diffuse.

4. Brain abscess.

5. Cerebellar abscess.

6. **Chronic adhesive middle ear catarrh** occasionally causes dull or even sharp earache. Prophylactic treatment of this condition is most important, because if neglected it causes permanent impairment of hearing. Removal of tonsils and adenoids early, in children suffering from repeated ear infection, is the best prophylaxis.

7. **Blue ear drum** is a rare condition in which the tympanum is filled with a thick chocolate-like secretion. Inspection shows the blue ear drum. It causes more of a fulness than an earache. Treatment is the same as for serous otitis media.

(B) External ear disease causing pain.

1. Inflammations

(a) Furunculosis

- (b) Eczema
- (c) Fungi
- (d) Erysipelas
- (e) Subperichondrial abscess
- (f) Herpes zoster auriculæ
- 2. Foreign bodies
  - (a) Inanimate
    - (1) Impacted cerumen
    - (2) Vegetable as peas, corn, beans
    - (3) Miscellaneous—stones, paper, pencils, etc.
    - (4) Epithelial plugs
  - (b) Animate
    - (1) Insects
    - (2) Worms
- 3. Trauma
  - (a) Burns
  - (b) Frostbite
  - (c) Pugilist ear
  - (d) Wounds—gunshot, stab, etc.
  - (e) Rupture of ear drum, penetrating wound, blow, skull fracture
- 4. New growths—carcinoma
- 5. Granulomata
  - (a) Syphilis
  - (b) Tuberculosis
  - (c) Blastomycosis
  - (d) Actinomycosis.

(a) **Furunculosis** of the external meatus is always located in the outer membranous portion of the meatus and the diagnosis can nearly always be made by eliciting pain by pressure upon the meatus or by movement of the auricle. If the furuncle is deeper in the meatus and large, it may push the auricle forward, simulating a subperiosteal abscess in acute mastoiditis. Both conditions may be present. Often furunculosis is associated with an acute or chronic suppurative otitis media. In these instances the signs of inflammation as given above are found in the external portion of the meatus and the indications of the middle ear disease are discovered with speculum and by means of tuning-fork examination.

The pain in furunculosis is often severe and out of all proportion to the clinical findings. It is referred to the ear and the side of the head, and often mastication is painful.

*Treatment.*—Prophylaxis. "Avoid scratching the ears with anything but the elbows" is trite but excellent advice. For itching ears use salicylic acid in alcohol (1:10 per cent). Swimmers may avoid furuncles if boric acid and 95 per cent alcohol (4:100) is used to dry the meati after coming out of the water.

The active treatment of furunculosis should always be conservative. My preference is to carefully wipe out the meatus and fill with  $\frac{1}{2}$  of 1 per cent yellow oxide of mercury in water-free lanolin. This procedure should be repeated daily by the physician until the furuncle ruptures or subsides. At home the patient should use wet hot dressings of generous size over the auricle constantly if the pain is severe. Sedatives may be prescribed, as acetylsalicylic acid, acetanilid, salicylates, even morphine. With this treatment the patient suffers usually two or three days, but recurrences are rare. In infants the same treatment may be used. Phages and anti-virus may be used. Five per cent carbol glycerin, 4 or 5 drops every three or four hours, may be tried in the ear early. When the furuncle has developed to a distinct white head, it may be incised with a cataract knife, using proper antiseptic precautions. Roentgen rays may be tried when the furuncle does not point and great induration is present. The dosage is usually about one-third erythema dose. Wick treatment is used by some otologists. Moist wicks are used, saturated with a weak solution of aluminum acetate or other astringent drug. Dry treatment is preferred by some. This may be carried out by blowing boric acid powder into the meati.

For recurring furuncles, good results are often obtained with autogenous vaccines.

(b) **Eczema** of the auricle and external meatus may occur in any form, but does not produce earache unless complicated by furunculosis or perichondritis. Itching is the chief symptom. The treatment (rather unsatisfactory) is both general and local, but does not fall properly under the title of this paper.

(c) **Fungi (Otomycosis).**—A soft, dirty, grayish, salve-

like substance may form in the external meatus. When this is removed, the canal wall appears raw and bleeds easily. This material recurs in a few weeks after cleaning if the canal is not treated. Subjectively the patient complains of a fulness, stinging or itching in the ear. The infection may be resistant to treatment. Usually a mild parasiticide is prescribed, as 2 to 10 per cent salicylic acid in 95 per cent alcohol. The ear is wiped out fairly dry and the patient instructed to fill the canal once or twice daily with the mixture. Hyposulphite of soda (0.2 in 30) may be tried. In a few days the fungus growth may be destroyed, after which it is well to have the treatment continued at weekly intervals for some time to prevent recurrence.

(d) **Erysipelas** of the auricle does not differ from erysipelas in other parts of the body. The pain may be intense in the involved region and the disease presents its redness, swelling, raised, red border and fever.

*Treatment.*—Prophylaxis and isolation from surgical and obstetric patients until lesions are healed. Locally, the treatment is ultraviolet irradiation of the area involved and of the normal adjacent skin at least 2 inches beyond the border. Roentgen rays are used not over one-fourth erythema dose. Evaporating lotions are applied ice cold by means of uncovered compresses. A 50 per cent solution magnesium sulphate may be used. Erysipelas antiserum preceded by an intracutaneous test of 0.1 cc. of the serum diluted 1:10 may be used. If the test is negative within fifteen minutes, the remainder of the contents of the ampule may be injected. The dose may be repeated daily for three days. If the test is positive, it might be well to try convalescent erysipelas serum rather than the serum derived from the animal, in amounts varying from 40 to 100 cc. Fever symptoms are treated as indications arise. Hypnotics, often paraldehyde (teaspoonful in a half glass of water), are used for obstinate insomnia, and stimulants for collapse.

(e) **Auricular perichondritis or subperichondrial abscess** is ushered in with pain over the auricle affected, the

pain depending on the severity of the infection and the area involved. The treatment depends on the extent of the lesion. If a relatively small area is involved, conservative treatment with wet dressings is indicated. If it is more extensive, it is best to incise early and drain with a small gutta-percha drain. Warm dressings are applied and the drain changed daily. The bandage should be rather tight. The principle is to save as much cartilage as possible because of the rapid cartilage necrosis and the consequent disfiguring deformity.

(f) **Herpes Zoster Auriculæ (Koerner's Syndrome: Hunt's Syndrome).**—Herpetetic eruption over the concave surface of the auricula and the external acoustic meatus may be associated with facial paralysis. The pain is burning in character. Since the pathology is thought to be a geniculate ganglion neuritis, the treatment is that of any neuritis. Remove foci and give salicylates. One to 5 per cent ammoniated mercury ointment may be tried locally.

**Foreign Bodies.**—Impacted cerumen is the most common foreign body but causes the least pain. If there is any pain, it is usually a fulness in the affected ear or occasionally an unpleasant sensation of something striking the ear drum with a change of position. Treatment consists in removal by syringing with an ear syringe, using warm water. The stream should be directed toward the upper portion of the canal while the auricle is pulled upward and backward. If several attempts prove unsuccessful, the patient is instructed to use normal salt or soda water in the ear twice daily and to return for a second syringing. The ear hook may be used if the operator is careful and skilful enough not to injure the delicate epithelium of the external meatus. The hook is placed over the cerumen, turned, and gentle traction is exerted. The cerumen, if dry and hard, is adherent to the dead surface epithelium. Therefore, the patient should be cautioned to hold still, and to swear, not jump, if hurt.

Vegetable foreign bodies, as peas, corn and beans, may swell after lodging in the external meatus and thus cause con-

siderable pain. They can usually be syringed out if found early. Otherwise they must be removed with a hook or ear forceps. Great care must be exerted to do no harm in treating foreign bodies. It is far better to leave any foreign body in the meatus than to injure the epithelial lining or push the object through the ear drum while trying to extract it.

Stones, paper and miscellaneous materials are often found in the external ear and may or may not cause earache. They are removed as described. Hard foreign bodies, when medial to the isthmus of the meatus, may be difficult or impossible to dislodge. A modified radical mastoid operation may be necessary. A considerable number of serious complications are seen each year because of clumsy attempts at removal of foreign bodies.

Epithelial plugs (cholesteatoma-like accumulations) are rare in the external auditory meatus, but may cause earache and impaired hearing if present. The treatment is to remove the mass by mechanical means or by a solution which is dehydrating, as 1 per cent salicylic acid in alcohol. After the canal is cleaned, the granulations should be treated until healed.

Live insects may be very painful as they hop up and down on the ear drum. A few drops of alcohol or chloroform quiets them, after which they are easily syringed out. In emergency, pouring water into the meatus will subdue these insects.

**Trauma.**—Burns demand no special consideration, as they are treated the same as burns elsewhere.

Frostbite frequently affects the auricles because of their exposed location. Instead of painful ears, the ears feel numb. They should be rubbed with snow or cold hands. This treatment restores the circulation. When the ears become painful they are treated as burns.

A prize fighter ear is usually caused by a blow on the auricle, or by a twist. Pain depends upon the amount of blood accumulated beneath the perichondrium, but is usually not severe. If the effusion is small, it should be treated conservatively and will absorb with a pressure bandage. If the

blood clot is larger, free incision through the perichondrium is necessary and a pack is inserted as in perichondritis.

Wounds need no special description.

Traumatic rupture of the ear drum by puncture wound, a blow on the ear, explosions, or skull fracture may be accompanied by severe pain in the ear. Treatment is to control the hemorrhage, if necessary, by sterile tampon. In most cases all that is necessary is to prevent infection to the middle ear by using sterile cotton in the external meatus. Treat middle ear suppuration if it occurs.

**New Growths.**—Epithelioma may attack the auricle or meatus. Pain is not a prominent feature. The treatment does not vary from the treatment of carcinoma elsewhere. Early excision or diathermy is indicated. If seen later, x-ray and radium may be tried. If the temporal bone becomes involved, the earache is one of the most terrible of pains and the treatment is unsatisfactory.

Endothelioma occurs in the ear usually secondary to parotid involvement.

Sarcomas, lipomas and neuromas are rare.

**Granulomata.**—Syphilis and tuberculosis may occur on the auricle, but pain is usually insignificant. Blastomycosis and actinomycosis may involve the ear and cause moderate earache. A biopsy is usually needed for the diagnosis. I recently diathermized a blastomycosis of the lobule of an ear which I felt sure was epithelioma without waiting for a biopsy report. I should have suspected blastomycosis because of the large amount of destruction in nine months' time. Iodides in massive doses daily for a long time are the sheet anchor of treatment of these mycoses.

(C) **Internal Ear Disease Causing Earache.**—Involvement of the labyrinth and brain due to middle ear disease has been discussed. There is no earache as a rule from internal ear disease caused primarily from meningitis, scarlet fever, mumps, measles, influenza or typhoid fever. There is only tinnitus.

## II. Reflex Aural Pain.

*Toothache* frequently causes referred pain to the ear. The wisdom teeth are the chief offenders, the lowers more often than the uppers. Impacted molars which are causing otalgia may be discovered by a skiagraph. The treatment is the extraction of the offending tooth or teeth.

*Acute tonsillitis*, peritonsillar abscess and post-tonsillectomy infection may give rise to earache, but usually there is no difficulty in the differential diagnosis and the treatment is self-evident.

*In parotitis* the pain may be referred to the ear, but diagnosis is simple unless the external meatus is encroached upon so much that the ear drum cannot be examined.

*Laryngitis* caused by tuberculosis, cancer or other granuloma may cause otalgia. In these cases there is usually hoarseness and when the larynx is examined, the lesion is found. Biopsy is often necessary to make the differential diagnosis. Disease of the larynx causes earache by irritation of the superior laryngeal nerve, a branch of the vagus. The treatment is self-evident but one point might be mentioned. In dysphagia the superior laryngeal nerve is sometimes isolated and severed. When isolated, it is pinched gently, which causes pain in the ear and proves that the proper nerve is about to be cut. This symptom is also used as a guide for nerve block in dysphagia.

*New growths* in the vault of the pharynx and in the retropharyngeal region often cause earache. This pain may come from pressure on the nerves in this region or by pressure on the eustachian tube orifice, causing middle ear disease. These tumors are treated surgically or with x-ray and radium.

Other conditions causing neuralgic pain in the ear are carcinoma of the superior maxilla, cancer of the tongue (posterior third), inflammation of the gasserian ganglion, cold air, anemia, hysteria and neurasthenia. Treatment consists in treating the etiological factor.





## CLINIC OF DR. CHARLES W. FREEMAN

### NORTHWESTERN UNIVERSITY DENTAL SCHOOL

#### PAIN IN THE DENTAL FIELD

PAIN in the dental field is usually definite in character and location, and in most cases the cause can be determined and readily eliminated by the available methods of diagnosis and treatment. Occasionally certain atypical and migratory pains require careful study for accurate determination of the cause and not infrequently search must be made outside the oral cavity.

Toothache is not in any sense a modern disease nor has its incidence been greatly reduced in modern times. It is, however, a preventable disease or rather it is a symptom of a pathological disturbance which to a great extent is preventable. Dental caries is probably the most common of all diseases and at the present time is not entirely preventable, but it can be controlled. Modern dental care which includes periodic examination of the mouth and teeth with proper control of caries by fillings should prevent entirely the development of toothache.

#### PULPITIS

Pain known as toothache is caused by an hyperemia of the dental pulp, that highly innervated soft tissue which is entirely enclosed within a pulp canal and surrounded by dentine. Its blood supply is by way of one or several small foramina at the apex of the tooth, a fact which precludes the establishment of collateral circulation, and consequently tends to complete infarction when the pulp is seriously disturbed.

When an inflammatory process develops as a result of irritation—traumatic, chemical, thermal or bacteriologic—the en-

closing dentine permits no expansion of the inflamed tissue and a sharp pain ensues. Such a pain may be steady or intermittent, sharp, dull or throbbing, depending on the local factors. It may be stimulated by a single sudden irritation, beginning as a sharp stabbing pain which gradually recedes. It may be aggravated by recurrent irritations, as in thermal shock where large metallic fillings are close to the pulp, the transmission of all extreme changes in mouth temperature repeat the insult to the pulp, thus further increasing the inflammation.

A steady pain of the same general type but without recurrent external cause generally indicates a partial degeneration or necrosis of the pulp. Infection may be present or absent within the pulp at this stage of degeneration. This pain occurs most frequently at night and there is at least a partial remission during the day, although the pain may be stimulated by outside irritations. Usually, in fact, such a tooth is extremely responsive to external stimuli and the patient is inclined to favor and protect it by chewing on the opposite side and avoiding extremes of temperature within the mouth. At night the pain is likely to be throbbing and the pulse can be distinguished by waves of increased pain.

Diagnosis of the cause of these pains is made by clinical study, augmented by thermal and electric tests of the suspected pulps. Often the patient can identify the offending tooth and clinical examination reveals an all too evident cause. The *x-ray* is not often useful, since pulp changes are not demonstrated on the *x-ray* film, although in pulpitis of long standing periapical bone changes may occur sufficiently to be recorded on the film while the pulp is still vital. The *x-ray* film is also useful in discovering hidden causes such as leaking fillings, undiscovered caries and, of course, is useful in ruling out other possible sources.

Occasionally the location of the pain is not definite and if an evident cause such as open caries is not discovered, it requires a careful *diagnostic study to determine the source*. Generally a delay of a day or two will permit further progress

of the pulp degeneration with consequent definite localization of the pain and at that time any doubt as to location and cause is removed.

The causative factor in pulp irritations may be the formation of secondary dentine such as occurs in connection with severe abrasion of the teeth. This secondary calcification may be so extensive as to completely obliterate the pulp chamber, the pulp receding as the secondary calcification takes place. This is an emphasized physiological action and normally occurs without pulp irritation, but may occasionally be responsible for severe pulp disturbances accompanied by pain.

In any pulpitis regardless of the cause, the recovery of the pulp is doubtful if the pain has been of long duration. The treatment consists of the extraction of the offending tooth or the surgical removal of the pulp with subsequent treatment of the pulp canal and placement of a root filling.

#### PERIAPICAL INFECTION

Pulp degeneration with eventual death of the pulp by infarction may be a rapid process accompanied by mild or severe pain symptoms just discussed, or it may occur with little or no pain and may be a very gradual process extending over months. Ultimately the death of the pulp does occur and a new type of pain may result. This is the pain connected with periapical inflammation and infection, and is of an entirely different character.

This pain may begin before the pulp degeneration is completed and this makes an accurate diagnosis difficult, because one type of pain is merging into the other, consequently the pain is not typical of either pathological condition. Usually the period of transition is not prolonged, since inflammation in the periapical region causes additional disturbance to the blood supply of the degenerating pulp and complete infarction rapidly follows. It should be reiterated that both these conditions may occur as a result of irritation without infection, but even if infection is not present in the early stages it almost invariably occurs later if treatment is not given.

Pain connected with periapical infection is distinguished from pain within the pulp by the character of the pain and the reaction to external stimuli. In periapical infection the pain is definitely one of pressure, it is generally well localized and a certain tooth is sore to percussion and pressure and the tooth gives a sense of elongation due to the pressure of confined fluids in the periapical space. At this period or a little later the gum tissues over the apex of the tooth also become inflamed and sore to pressure.

A controlled inflammatory process probably occurs in the periapical region in every case in which the pulp dies or is artificially removed. If infarction of the pulp occurs without bacterial invasion or if the pulp is removed surgically by dental methods, the disturbance of the periapical tissues and the consequent pains are slight and transitory. Occasionally chemical irritation with considerable pain occurs during the treatment of a tooth with certain drugs used for sterilizing the root canal. This also is transitory unless metastatic infection occurs.

The initial periapical bone changes which can be depicted on the x-ray film are probably caused by the inflammatory reaction with pressure resorption of the bone. When infection occurs bacterial liquefaction of the bone follows and a definite bone cavity develops. Coincidentally, an inflammatory proliferation of the connective tissue of the peridental membrane occurs, and this proliferated tissue eventually becomes the so-called "granuloma" of the chronic periapical infection. The granuloma is a protective rather than a destructive tissue and serves to wall off the infection, and under favorable conditions the infection may actually be eliminated with eventual regeneration of bone.

During the early stages of the acute periapical disturbances infection is not under control and the severe pain increases and continues for several days. Unless relief is given by treatment through the root canal the infection develops to a point where evacuation through the bone relieves the severe pressure. In the occasional case the infection is controlled

by the tissue response and spontaneous recovery from the acute phase of the infective process occurs.

When the acute infection continues to the localization of pus there is usually a definite time at which the severe pain from confined infection is relieved by evacuation through the bone. The pain then becomes more generalized, but the tooth is no longer sore, for the tissues overlying the bone in the periapical region are now exhibiting the symptoms of acute infection. General toxic symptoms also increase at this stage, but such symptoms seldom occur while the pulp is still vital regardless of the amount of pain which may be present.

After localization of pus beneath the periosteum the proper treatment is evacuation of the pus by incision or if untreated, there is usually an eventual spontaneous evacuation. Any delay in drainage after localization is dangerous, for subperiosteal accumulation of pus seriously interferes with the blood supply to the bone and may result in serious bone disturbance.

Pericoronal infections about partially erupted teeth, and occasional lateral abscesses due to deep pyorrhea pockets alongside the root of the tooth may also exhibit some of the symptoms described in periapical infections. Generally the first phase of the infection with the typical soreness of the tooth to percussion is absent in such infections, since they do not begin in the apical region. They are also more likely to end in spontaneous drainage, since the initial infection is not located deep within the bone.

A large percentage of the pains in the oral cavity are of the types just discussed. Accurate diagnosis is usually possible at the first clinical examination. Occasionally observation for a day or two is necessary to determine the exact source of the pain, but since both types of disturbances are progressive in character any uncertainty may be eliminated by a short period of clinical observation. After the cause of a pulpitis or a periapical infection has been determined definite treatment is readily planned and practically always effective.

## MAXILLARY SINUS INFECTION

Maxillary sinus disease is occasionally of dental origin but the initial cause is more frequently nasal. Pain in the dental field may be caused by sinus infection regardless of the original source, since the roots of the upper teeth are frequently in close proximity to the maxillary sinus. In addition to the common symptom of a general feeling of pressure in the sinus region there may be a definite sense of soreness about the teeth. This pain is very similar to a beginning periapical infection and may occasionally appear to be localized definitely in an upper bicuspid or molar tooth.

x-Ray studies may not always rule out the teeth, and pain tests are only an indication, not an accurate diagnostic aid. Adequate sinus examination by a rhinologist should be obtained in cases of uncertainty. On the other hand, a periapical dental infection may simulate a maxillary sinus infection and in any uncertainty a careful dental examination is essential. Probably a careful study of all the upper teeth should be routine procedure in all maxillary sinus infections.

## UNERUPTED AND IMPACTED TEETH

Vague pains about the face and jaws are frequently attributed to the presence of embedded and unerupted teeth. No satisfactory explanation of the mechanism causing such pain has been advanced, but their removal is often recommended in the expectation of relief.

Unerupted teeth may become infected if there is direct communication with the mouth cavity and infrequently they become infected when no such communication exists. Such an infection runs a typical course and is often responsible for local pain, but it is the typical pain of local infection and is accompanied by clinical signs of infection. Pains which are intermittent in character or sharp shooting neuralgic pains are not caused by local infection about unerupted teeth.

Direct contact between an unerupted tooth and its immediate neighbor may cause a pressure resorption of the root of the contiguous tooth, thus setting up a severe pulp irrita-

tion with accompanying pain. Such resorptions can usually be identified by radiographic study and the usual symptoms of pulpitis are generally definite and well localized. Caries occurring in the partially erupted tooth or in its immediate neighbor as a result of food impaction may occasionally give the same symptoms of pulpitis. The cause is always demonstrable by radiographic and clinical examination when this does occur.

There is no valid reason to believe that the presence of an unerupted tooth in itself causes any pain, although some clinicians have expressed the belief that this does occur. It is explained on the basis of intermittent efforts on the part of the tooth to erupt, the eruptive force causing pain by pressure on adjoining structures. This hypothesis does not appear tenable, for pressure resorption occurs in advance of eruption and if bone structure is the only impediment to eruption, that bone resorption would be slow and painless. Innumerable clinical cases occur in which teeth, which are prevented from erupting, remain for years with no painful symptoms.

Vague pains and other nerve disturbances in the facial region which cannot be satisfactorily explained should not be attributed to unerupted teeth simply because they are found to be present. Careful examination may reveal the presence of caries, resorption of the contiguous tooth or pericoronal infection, but few, if any, other pains are caused by unerupted teeth. Follicular cysts occasionally develop about unerupted teeth, but they are painless unless infected. Supernumerary teeth and composite odontomes are frequently present about the jaws, but are not responsible for pain symptoms except under the same conditions which cause pain about unerupted teeth.

#### NEURALGIA

Pains generally classified as neuralgia may be considered as major and minor neuralgia. Major trifacial neuralgia or the *douloureux* exhibits typical symptoms and a definite diagnosis is practically always possible. Sphenopalatine neural-



gia is also typical in its symptoms and although infrequently encountered the diagnosis can generally be made on the basis of symptoms.

Minor neuralgia about the teeth and jaws is probably most often a pain symptom with a definite local cause which can be discovered by painstaking search and should not be classed as a neuralgia. Dental causes are then the most frequent sources of these pains in the regions innervated by the second and third divisions of the fifth nerve. These causes are frequently obscure and it requires a most careful survey of every possible source to determine the causative factor. This survey should include complete radiographic study of the jaws including the edentulous areas.

Such a study will include a search for dental caries, infections, retained roots, supernumerary and impacted teeth, imperfect and irritating dental restorations and any abnormality of bone structure. Disease of the maxillary sinus should be considered and ruled out as well as any nasal disturbance which might be a contributing factor.

Infrequently such pains may be caused by local nerve irritations in the region of a previous operation. Not only fractured retained root tips, but rough margins of alveolar process may be acting as local irritations. These occurrences are not common, for usually root fragments are exfoliated or encapsulated, the encapsulated fragments becoming surrounded by a low-grade chronic infection which does not cause pain. Rough margins of alveolar bone following extraction of teeth are generally resorbed or exfoliated and the tissues make the necessary adjustments without painful sequelae.

Several clinicians have reported the relief of such pains by minor operations which released small nerve filaments from the pressure of contracting scar tissue where operation had previously been performed, especially in the regions where impacted teeth or large cysts had been removed. This is a plausible explanation and possibly has some basis of fact, although such cases are so infrequent that there is considerable doubt of their actual significance.

## EXTRAORAL CAUSES

Among the extraoral causes for pain in this region intracranial disturbances, especially brain tumors, must be considered as the most important. On several occasions I have been requested to remove impacted teeth for the relief of severe pain, when a more complete medical and neurological examination proved the source of pain to be a brain tumor.

Traumatic causes are usually self-evident and easily determined as the cause of pain. Tumors along the course of a nerve occasionally cause pain, but when this does occur it is a different type and not easily confused with pain of dental origin.

Arthritis of the temporomandibular joint is infrequent and the pain is definitely localized and is increased with functional movement. Pain which is due to changed relations of the structures of the temporomandibular joint, as a result of the loss of teeth or changes in occlusion due to wear, are usually referred to the region of the ear rather than the oral cavity.

## BURNING TONGUE

An affection of the nerves, described as burning tongue, occurs infrequently. It is not a pain, but rather an unpleasant sensation, quite constant but with remissions. I have seen this most frequently in women during the menopause and it may probably be attributable to derangement of the entire nervous mechanism rather than to any local source. It has been suggested that the explanation may be based on electrophysical reactions induced by the presence of metallic filling in the teeth. There has been no verification of this hypothesis.

## SUMMARY

The pains about the oral cavity may be grouped as:

- 1 Irritations and infections of the dental pulp.
- 2 Infections and inflammations at the root ends.
- 3 Disturbances about unerupted teeth.
- 4 Pains not of dental origin.

The diagnosis of the cause of such pains is usually possible with the available clinical, radiographic and laboratory methods. Occasional severe pains occur in which the cause is obscure and continued search may fail to reveal any local cause. When such pains are of dental origin and the proper diagnosis is made, definite treatment may be adopted which will rapidly and effectively eliminate the pain.

## CLINIC OF DR. WALTER R. FISCHER

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#### RELIEF FOR PAINFUL FEET

THE successful relief of pain in the feet requires as the first step the correct interpretation of the pain. A thorough knowledge of factors that produce pain in this part of the body is of the greatest importance for the analysis of each case presented. The need of a careful general survey of the patient cannot be too greatly emphasized. Pain in the foot may be the manifestation of some constitutional disease or the result of some local disturbance. One can distinguish only by a thorough physical examination. A systematic study should be made of the character, location, time of occurrence, duration and mode of onset of the pain together with a careful consideration of the associated factors such as systemic disease and local changes or abnormalities.

The things that must be taken into consideration in the history of every case are the age, sex, occupation, weight, the possibility of systemic disease, disturbances in posture and the elements presented by the feet themselves, along with the type of wearing apparel.

The cause of the pain varies to a great extent with the age of the individual. For instance, in the very young child one may find the cause to be a weak pronated foot due to faulty use or it may be associated with a deformity of the lower extremity such as genu valgum, knock knee, which disturbs the line of weight upon the foot. The older child or adolescent may suffer from foot strain brought on by the more

strenuous athletic games or the burden of occupation. Discomfort in middle-aged adults may result from obesity, arthritis or faulty shoes, while persons in advanced age may complain of trouble appearing as the manifestation of vascular disease. In other words, the age is more or less an index of the kind of trouble that is possible.

A very important distinguishing feature in the analysis of foot discomfort is the sex of the person. Women make up the great majority of individuals seeking relief and in a large percentage of the cases the modern style shoe is responsible for the production or aggravation of painful foot disturbances.

Occupation plays an important part in the production of pain in many ways. It may call for long hours of standing, which is usually done with the feet in a pronated position, thus weakening by exhaustion the upward pull of the adductor muscles of the foot. A patient's duty at work may require the lifting and carrying of heavy objects, walking over rough and irregular tracts of ground, or walking on hard pavements for many hours. A person who has escaped trouble for many years at a desk job may be transferred to a position that requires a great deal of activity upon the feet and as a result suffer great discomfort.

Since the functions of the foot are to support and move the body about, the influence of weight in every instance must be determined. Given a normally functioning foot with an extra heavy body superimposed, there is bound to be sooner or later a change in the comfort of the foot, and from no other cause than the additional weight burden. When the factor of excess weight has added to it the presence of a pathological condition in the foot such as for example arthritis, the symptoms of distress can be expected much earlier.

The presence of systemic disease as a source of discomfort can be only too plainly portrayed in the arteriosclerotic, the diabetic, the nephritic, the cardiac and the arthritic patient. As a point of emphasis on the importance of a careful consideration of the influence of systemic disease, suffice it to say that the most brief discussion of the manifestations of

constitutional disease in the foot would require a prohibitive length of time.

The chief elements presented by the feet alone in the production of pain can be classed as muscular disturbances, neglected sprains, inflammatory lesions and deformities. The influence of wearing apparel, since it is a most constant covering of the foot and since its shape is governed by style instead of the anatomical characters of the foot, is one of the most common factors in the production of pain and deformity. The present-day feminine type of style shoe with its high, narrow, wobbly heel, short, low, pointed vamp, is probably responsible for more discomfort than any other single factor.

The cases presented in this clinic represent disturbances in the anterior part of the foot. The pain in such instances may vary from a mere feeling of discomfort, numbness, or dull ache, to a sharp stabbing or burning or even a severe cramplike nature. It may be ill-defined and vague in its distribution over the region of the ball or it may be definitely localized in the region of one of the metatarsophalangeal joints or in one of the toes. Too, it may be associated with the symptoms of inflammation or deformity.

The treatment for the relief of pain in every instance depends upon the accurate determination of the cause of the pain and the elimination of that cause. In the obese individual one must reduce the weight; in the weak foot one must institute correct postural habits in standing and walking along with corrective exercises; while in the arthritic, the arteriosclerotic and the diabetic patient one must direct the treatment at the general as well as the local condition. A careful study of the causes of painful feet will convince any competent physician of the fallacy of focusing the attention upon the feet alone in an attempt to establish satisfactory remedial measures.

**Case 1** Mrs. H. S., aged thirty-six, weight 206 pounds, height 5 feet 8 inches, housewife. On April 27, 1935 the patient complained of extreme soreness on the ball of the left foot in the region of the base of the second toe. The disturbance was of two years' duration and was always considerably

worse after a great deal of walking. The annoyance of the pain had become so severe the patient volunteered the statement that she wanted relief regardless of the type of treatment or shoe required. Examination revealed tenderness on pressure beneath the second metatarsophalangeal joint, along with limitation of plantar flexion of all the toes. The shoe constantly worn by this patient had a very narrow heel  $1\frac{7}{8}$  inches high with a short low-pointed vamp. An outline of the sole of the shoe showed it to be much narrower than the bearing surface of the foot. Until one month before examination the patient had weighed 223 pounds. According to a standard weight chart her weight should have been 140 pounds. A diagnosis was made of foot strain manifested by pain in the anterior part of the foot.

The factors in the production of the pain were determined to be 83 pounds of excess weight until one month before examination and a high heel shoe with a too small compartment for the toes. A shoe heel  $1\frac{7}{8}$  inches high continually throws the weight forward on the anterior part of the foot and when the toes are crowded together by the front part of the shoe their normal activity is greatly limited and limitation of motion and muscular atrophy soon follow. The function of the toes in aiding the foot in walking is seriously impaired.

The management of this case consisted of weight reduction, a low broad heel on the shoe and a wide compartment for the toes, along with exercises. Relief is invariably the rule when such changes are made. Because of the acute symptoms, it is often necessary to keep the patient off the feet for a short time in order to allow the inflammatory reaction from injury to subside. Pain in the forepart of the foot in such cases as the above may be a mere feeling of discomfort, a dull aching pain, a burning sensation or even a sudden spasmodic cramplike pain in the region of the ball and in conjunction with it there may be a numbness or tingling sensation in one of the toes.

**Case II.**—Mrs. A. D., aged fifty-five, weight 110 pounds, height 5 feet 5 inches, housewife. On August 10, 1934 the patient complained of an aching pain across the ball of both feet. The pain had been present for two or three months but was much worse the last fourteen days and was most noticeable in the left foot. The removal of her shoes gave no relief. Upon retiring at night the pain slowly subsided. She also complained of stiffness in her knees which was most marked after rising from a sitting position. Examination of her mouth revealed 3 gold crowns. x-Ray examination of these teeth showed all to be devitalized and abscesses at the bases of 2 of them. Manipulation of the great toe of the left foot produced pain in the region of the metatarsophalangeal joint. Her shoes were the typically conventional type with short pointed vamps and narrow heels 2 inches long.

The treatment of this patient consisted of rest periods off the feet, contrast baths, removal of all known infected teeth, and a low heel, broad toe shoe.

On August 31, 1934 she reported back for observation having carried out all previous instructions given her. She was greatly improved.

The impression of Case II was arthritis of the feet in the presence of foci of infection and faulty shoes.

Trouble is almost inevitable when the foot has added to its normal burden the presence of arthritis and a shoe that interferes with its function as a weight-bearing organ. This patient at the age of fifty-five years had arthritis in the feet and knees in the presence of definite foci of infection in the mouth. The management of such a case for the relief of pain in the feet certainly necessitates the installation of anti-arthritic measures which, of course, consist of rest, improvement of function in the feet along with physiotherapy and attention to all foci of infection. There are certain factors one must seriously consider in attempting to obtain relief for the patient with arthritis in the feet. In obese individuals, the extra burden of excess weight upon the inflamed joints must be removed to the greatest extent possible. It is needless to mention the practical good that comes from the removal of foci of infection throughout the body. The common conventional shoe so universally worn by women with its high, narrow, unstable heel and narrow pointed vamp must be promptly replaced by one that will permit more normal function in the foot and more normal distribution of the weight. The too thin sole that allows trauma from the hard present-day pavements is better replaced by a thicker one that affords more protection to the inflamed joints of the foot. In mild cases of arthritis where a flimsy type of shoe is worn, a good strong shoe with a stiff shank will often give enough relief as a single factor to increase the patient's comfort many degrees. Those individuals who have occupations that keep them for many hours upon their feet need in addition to other antiarthritic measures, rest periods during the working hours. In many cases it may be necessary for the patient to arrange



hip joints. Examination revealed marked limitation of motion in both great toe joints in all directions but especially in dorsal flexion. After careful consideration of her general condition a diagnosis of hallux rigidus due to productive arthritis of the first metatarsophalangeal joints was made. Anti-arthritic measures were instituted and for local treatment the patient was fitted with a pair of low, broad heel shoes with broad toe compartments. Underneath the great toe joint and just distal to it a wedge of leather  $\frac{1}{4}$  inch thick was placed in the sole of the shoes. After a preliminary rest period to quiet the acute symptoms of arthritis the patient was allowed to walk about in the newly prepared shoes. Since she has worn the modified shoes, she has reported back a number of times in the last thirteen months and in each instance she reported that she had never been so comfortable for years.

The wedge in the sole of the shoe stiffens the sole and limits motion in the great toe joint. In such cases of hallux rigidus, Whitman mentions the use of the wedge on the inner side of the sole to stiffen it and limit motion in the great toe joint.

**Case VI.**—Mr. L. B., aged fifty-five. On January 28, 1933 he appeared for treatment of a "bunion" on the right foot which he said had been present for several years but had become inflamed and painful the last six weeks. Examination revealed enlargement of the great toe joint of the right foot with a reddish circular area on the skin of the median part of the joint. The first impression of this case was that the lesion presented was due to a tight shoe. Warm moist applications and rest without the shoe made little change in the condition. A thorough examination of the patient was then made and revealed the following findings: Blood pressure, systolic 162, diastolic 88; blood sugar 333.2 mg. per 100 cc. of blood; urine showed 1 plus sugar; condition of cardiovascular system showed evidence of arteriosclerosis. Prompt attention was then given to his diabetes and arteriosclerosis with the result that he improved. He was not seen for two years. He returned for further treatment on April 23, 1935. At this time there was definite gangrene of the toes of the right foot. On May 3, 1935 his right leg was amputated because of spreading gangrene.

The significance of this case is the fact that the patient totally unaware of the presence of arteriosclerosis and diabetes was seeking relief for a painful disturbance in the foot. It shows emphatically the absolute necessity for a complete physical checkup in all cases presenting painful foot disturbances.

**Case VII.**—H. B., male, aged thirteen, weight 143 pounds, schoolboy. On April 29, 1933 this boy was brought in by his father because of a painful swelling on the dorsum of the left foot over the second and third metatarsal

bones. The condition had appeared gradually and was present for about two weeks. There was no history of injury. Because of a disturbance in the left hip joint this patient had placed no weight upon the left foot for many months prior to December 3, 1932. From December 3, 1932 to April 29, 1933 he had been walking. Examination revealed an overweight boy thirteen years old with a tender swelling over the dorsum of the left foot. x-Ray examination revealed a fracture with callus formation just distal to the middle of the second metatarsal bone. The diagnosis was march foot resulting from overuse of the foot following a long period of inactivity with the contributory factor of excess weight. The treatment consisted of rest off the foot and later exercise and gradual increase in the use of the foot. Complete recovery resulted.

A number of cases of march foot were reported by Speed and Blake in 1933, but in each instance the patient was over twenty years of age. They explained that "The condition has been well recognized for many years, especially by the German and French military surgeons, who frequently encountered it among their troops after strenuous duties or long marches."

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## CLINIC OF DR. G. K. FENN

### ST. LUKE'S HOSPITAL

#### PAIN SIMULATING THAT PRODUCED BY CORONARY DISEASE

IN collecting material to show causes for pain apart from coronary disease, one is astounded by the multiplicity of causes that present themselves. In many instances the pain is the result of a disturbance of the coronary circulation, but without coronary disease as such disease is usually considered. The latter causes have no place in this discussion, and I shall present no case records bearing upon them. I feel constrained to mention a few of them, because of their frequent occurrence. Hypotension is often accompanied by an anginal type of distress. As the coronary circulation is largely dependent upon the blood pressure, such distress is not surprising. Hypothyroidism is frequently attended by similar distress, even when the blood pressure is relatively undisturbed. The reason here is not quite so clear, but probably arises from the lowered metabolism. Neurocirculatory asthenia or the effort syndrome may be associated with severe pain, sometimes simulating coronary occlusion. Severe anemia may produce anginal pain. Some years ago anginal pain was a common symptom in pernicious anemia. This distress is doubtless due to anemia of the heart muscle as a part of the general anemia.

There are other causes of pain that have their origin in the heart or coronary circulation, but with these few examples we shall proceed to a consideration of causes that are entirely extracardiac. One of the most common sources of confusion in this regard is the pain arising from osteo-arthritis of the spine. Scarcely a week goes by that one is not confronted with the

necessity of differentiating between this disorder and angina pectoris. This arthritic pain may be referred over a large area of the chest, and to the shoulder, and greatly resemble anginal pain. It comes on as a result of exercise, occurs usually in patients past middle life, both of which add to the similarity. Suspicion will be aroused, however, by the fact that the pain is more constant than anginal pain. The pain is accentuated by exercise involving the upper extremity and is accentuated by standing or lying in certain positions, while it is relieved by assuming other and often more uncomfortable positions. These observations will point to the true source. Examination will show a relatively normal cardiovascular system, and usually evidence of arthritis elsewhere. An x-ray of the spine will show pathology in that region.

Case I.—A woman of sixty-eight years gives a history of pain in the left chest and shoulder. This has been present intermittently for six years. She notes the pain is worse for several days after exercise such as housecleaning. There are times when the pain is absent for weeks, but when it reappears it is constantly present in varying intensity for days at a time. Sleeping on the left side seems to aggravate the pain, but sleeping or lying in bed on the back with the left arm extended above the head gives relief. This patient has been told she has angina pectoris, and has been receiving treatment. Examination shows cardiovascular system that is relatively normal for the age. There is a bit more than ordinary of arteriosclerosis. Exercise, such as walking up a stairway, brings no immediate increase in pain. There is evidence of considerable bony enlargement in the fingers and toes. An x-ray of the spine shows spicules and bridging of the dorsal vertebrae. Salicylates temporarily relieve the pain. Three years later the pain is unchanged or slightly better, and the patient has recently successfully combated a bronchopneumonia, a fair accomplishment for a patient of seventy-one years and a fair argument for a pretty sound cardiovascular system.

*Acute fibrinous pericarditis* with its attendant pain, shock, fever and leukocytosis and elevation of the pulse rate, may easily be mistaken for coronary disease.

Case II.—A young woman of twenty-six had been subjected to an abdominal cesarean section because of an acute toxemia of pregnancy. There was an immediate relief of the toxemia and seventeen days following the operation the patient was enjoying excellent health. On this day she was seized with a sudden severe pain in the precordial region. The pulse rose rapidly to 130, the patient became pale and slightly cyanotic. The temperature rose to

02° F., and the following day there was a marked leukocytosis. No friction rub was heard. The picture closely fitted that of a coronary occlusion, except for one symptom. There was rather severe pain along the left trapezius ridge. This did not rule out coronary pathology, but it raised a strong suspicion of pericardial or pleuropericardial inflammation. On the following day there was a considerable increase in cardiac dullness, with signs of pericardial effusion. x-Ray confirmed the heart size and a diagnosis of pericarditis was justified. The patient made an uneventful recovery.

*Pulmonary embolism* when not immediately fatal produces a train of symptoms strikingly similar to those of coronary occlusion.

**Case III.**—A woman of thirty-two, who had rheumatic carditis with mitral stenosis since childhood, came in because of tachycardia and weight loss. In addition there was great fatigue and occasionally a slight elevation of temperature. She was married and had gone through two pregnancies without incident. A subacute bacterial endocarditis was suspected, but the suspicion could not be confirmed. The patient continued to grow worse and a short time later it was discovered that she was again pregnant. A therapeutic abortion was decided upon and she was hospitalized for this procedure. At three o'clock in the morning of the day set for operation she had a sudden excruciating pain in the left chest. This was accompanied by an extremely rapid pulse, 160 to 180, marked dyspnea, pallor and cyanosis. She was extremely apprehensive and was quite convinced that she was dying, a symptom so common in coronary disorders. A diagnosis of coronary embolism was made, assuming that there was present the endocarditis which had been suspected. A pulmonary embolism was considered, but we lacked a good source for the embolus unless we assumed a right heart endocarditis. A few hours following the onset the patient spat up blood. This would fit into either picture. The pain persisted for several hours, and on the following morning a definite area of consolidation was made out in the left upper lobe posteriorly. This was most confusing until about thirty hours after the onset she began to bleed from the uterus. We were now furnished with the source of the pulmonary embolus which the condition proved to be. She aborted spontaneously, and had as a further complication a thrombophlebitis of the left leg, but made a good recovery.

There is a certain variety of pain associated with mediastinitis that occurs uncommonly but is very striking when encountered. I have seen but three cases of such pain. This phenomenon occurs in connection with mediastinal adhesions about the base of the heart. In my own cases it has been associated with adherent pericardium of rheumatic origin. The x-ray shows a partial obliteration of the upper part of

the mediastinal cavity. My cases have all occurred in individuals under twenty-five years of age. The pain is sudden in onset, very severe, and is located beneath the sternum. It has a typical anginal radiation and is associated with dyspnea and pallor. I have not seen cyanosis. The attacks of pain are paroxysmal in character and are rather evanescent and seldom last more than ten to twenty minutes. The patient is rather prostrated following the attack, but is relatively free from pain. They seem most likely to occur at night. In two of these three patients the attacks became progressively more infrequent and finally disappeared. I do not know the outcome of the third case. I have been told that similar attacks of pain occur in certain instances of high-grade mitral stenosis with great dilatation of the left auricle, but I have not encountered such patients.

*Spontaneous pneumothorax* with sudden onset will occasionally offer a diagnostic problem. This accident is commonly attended by severe pain along the costal border on the side in which the rupture occurs. In left-side pneumothorax it may resemble the pain of coronary occlusion. The acute pain is frequently succeeded by a sense of oppression that adds to the confusion. The onset of the pain is followed by a sudden acceleration of the pulse, a fall in the blood pressure, pallor, cyanosis and symptoms of shock. Dyspnea may be most severe. Examination of the chest will ordinarily reveal the cause of the difficulty. Pneumothorax with insidious onset may show no distinctive findings for several days. With sudden onset the classical hyperresonant or tympanitic chest may not be found. Air in the pleural cavity under certain degrees of pressure will produce a high-pitched tympanitic note that resembles dulness. The ruptured side, however, will be found fairly well fixed. The breath sounds will be impaired, and the heart dulness will be obscured or pushed to the opposite side. The x-ray will substantiate the diagnosis.

It would seem difficult to confuse traumatic pain with that of cardiac origin, and yet we have in our records a case of a physician who came in with his own diagnosis of angina

pectoris or coronary occlusion. He had a steady pain in the left chest. This pain had persisted for almost two days. It was present when he awoke one morning and became worse on exercise. This increase in pain on exercise was a constant feature. There was no shock or disturbance of cardiac rate or rhythm, but he became nauseated as the pain increased. Examination showed a sound cardiovascular system, but a great deal of tenderness over a limited area in the left chest. The x-ray revealed a fractured rib. It was impossible to determine how or when the accident occurred.

*Fibrinous pleurisy* not infrequently has as its initial symptom sudden, severe pain. This pain may originate in the chest or it may be first felt in shoulder or neck, depending upon the site of the inflammatory process. There appears to be dyspnea, but in reality the breathing is shallow and rapid rather than difficult. While the steady boring pain may resemble that of a coronary attack, the lancinating pain occasioned by a deep breath, will direct attention toward a fibrinous pleurisy and a friction rub will usually be heard if sought for at frequent intervals.

In a similar manner does lobar pneumonia occasionally introduce itself, with a steady boring chest pain of sudden onset. This together with the rusty sputum and the increased respiratory rate often raises a suspicion of coronary disease. The acute infectious nature of the disorder is usually recognized within the first twenty-four hours, and in the majority of cases unmistakable physical signs of pneumonia will appear by the end of the first day. This latter statement is by no means always true. We have numerous records in which the entire pneumonia showed a minimum of physical signs, and the x-ray findings were responsible for the diagnosis.

It would seem almost unnecessary to mention the pain of luetic aortitis and aneurysm in this connection, yet these conditions have been confused with angina pectoris and coronary disease. A careful physical examination will serve to differentiate.

So far I have presented records of pathology in and about



the chest as a cause of anginal pain. I have a few more illustrations of pathology outside the chest that has produced this picture. In a small percentage of peptic ulcers the first indication of their presence will be a perforation into the peritoneal cavity. This accident may be mistaken for a number of things, among which is coronary occlusion. The sudden onset of excruciating pain high in the epigastrium and radiating upward, the profound shock and the elevation of the pulse rate often justify this suspicion. Subsequent developments when sought for will correct the error.

**Case IV.**—A man of forty-two years, who had an old rheumatic carditis, was suddenly seized with excruciating pain high in the epigastrium. The pain radiated upward into the chest and into the right shoulder. When first seen he was in a state of shock, was pale and prostrated, and the pulse was 120 and thready. Blood pressure had fallen from 130 to 90 mm. Pain was severe and continuous. Respirations were shallow and rapid. There was a suspicious rigidity of the abdominal muscles but not enough to prevent a diagnosis of probable coronary occlusion. Four hours following the onset of the pain the abdominal rigidity had become unmistakable, and in six hours it was sufficient to change the diagnosis. By this time the pain had begun to move downward into the abdomen. The temperature did not rise above 100.5° F., and the highest preoperative white count was 11,000. Seven hours after the initial attack the abdomen was opened and a perforated ulcer was found. The patient made an uneventful recovery. This patient had been under observation for several months preceding the perforation and the presence of ulcer was not suspected.

Another patient that caused a few uneasy days was a man who was hospitalized because of an accident. There was no previous history of heart disease, but while lying in bed he developed an annoying pain in the left chest and shoulder. Realizing the frequent occurrence of thrombosis in patients who are bedridden, the question of a coronary thrombosis was immediately raised. Probably because of the frequent examinations of the cardiac area, the patient became "heart conscious," a condition which had not existed before. Nothing was found to substantiate the diagnosis of coronary thrombosis, and the condition subsequently proved to be a subdeltoid bursitis.

Latterly, we are likely to look upon the diagnosis of "acute

indigestion" with some suspicion. It is true that many, perhaps most, deaths from "acute indigestion" are coronary accidents, but we must not overlook the fact that minor disturbances of the gastro-intestinal tract may produce symptoms closely resembling coronary disease. The most severe abdominal pain may result from the distention of the spastic colon. Gas imprisoned in the splenic flexure will produce pain radiating upward into the chest and in addition will produce dyspnea, pallor and elevation of the pulse. To add to the difficulty of differentiation it must be remembered that in the anginous patient, gaseous distention is capable of producing the attack of angina pectoris. In such situations one is confronted with a delicate diagnostic problem.

Finally, diaphragmatic hernia has been a source of anginal pain. In those cases with which I am familiar the hernia has been situated at the esophageal ring. The x-ray has confirmed the diagnosis. In the cases of Drs. Portis and Bettman surgical repair of the hernia has abolished the anginal symptoms.

This list, I believe, represents the most important situations in which coronary disease may be justly suspected. I would call your attention to the fact that there are pitfalls for you on both sides of the diagnostic fence. Treating a coronary occlusion as an acute fibrinous pericarditis and allowing full liberty with the subsiding symptoms would be likely to result badly for the patient. On the other hand, treating a perforated ulcer as a coronary occlusion would almost certainly result fatally. A correct differential diagnosis is a most comforting thing.



## CLINIC OF DR. N. C. GILBERT

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#### TREATMENT OF ANGINA PECTORIS

BEFORE discussing the treatment of angina pectoris it will simplify the problem if we first make clear just the clinical syndrome we are referring to when we speak of angina pectoris, and if we review briefly some of the conditions predisposing to the attacks of anginal pain which have a direct bearing upon the treatment. We must also make certain that angina pectoris is clearly differentiated from coronary thrombosis. Just as in coronary thrombosis, the outstanding symptom is pain and pain which differs in no way from the pain of coronary thrombosis, except as to its duration. As in coronary thrombosis, also the pain is due to a blood supply to the heart muscle which is inadequate for its needs.

In coronary thrombosis there is an actual occlusion of one of the coronary arteries by a thrombus within its lumen. There results an interference with the blood supply to some portion of the heart muscle which persists. The extent of the area involved and the amount of anatomical damage and its permanence depend upon the position of the thrombus in the arterial tree and upon the ability of anastomoses, collateral circulation and the thebesian circulation to provide some degree of blood supply in the muscle affected. The amount of damage done may be only slight in some few favored cases, but it is usually enough to produce continued subjective symptoms and to impair the function of the heart to the extent that there are objective evidences of cardiac insufficiency. In some cases the amount of damage done is such as to be im-

mediately incompatible with life or to produce a fatal result in a very short time.

In angina pectoris the attack of pain is not due to the anatomical occlusion of any particular vessel immediately preceding the attack. The adequacy of the coronary circulation in the hearts involved varies through a wide range, but it is not permanently altered to any appreciable degree by any one attack. Whatever the condition of the coronary circulation may be, the pain occurs when the metabolic needs of the heart muscle are increased out of proportion to the blood supply available at the moment. The attack is of short duration and ceases when the demands upon the heart muscle are decreased, or when the blood supply is adjusted to meet the demands. Between the short attacks the patient is in what is a normal condition for the individual.

There are not any characteristic objective findings. It is probable that repeated short attacks may in time result in permanent myocardial damage. It is also probable that an attack may persist long enough to result in ventricular fibrillation and death.

There is a zone of common ground of indefinite breadth where it is difficult to differentiate between the two conditions in the first attack or in some individual later attacks. A coronary thrombosis may occur with very slight or moderate pain, or pain of very short duration with very little in the way of objective findings and still have even fatal consequences. The final outcome of recurring attacks of angina pectoris is very likely to be a coronary thrombosis and such a coronary thrombosis must be kept in mind in observing the recurrent attacks. In any case of doubt, the prudent procedure is to treat the case as one of coronary thrombosis until it has been proved otherwise.

Aneurysm, or a syphilitic aortitis without aneurysm, may be productive of substernal pain and should be differentiated. As a rule, the pain is quite different and whether only a dull ache or a very severe pain, is more prolonged and is not a paroxysmal attack precipitated by some definite cause. An-

ginal attacks may co-exist, especially if an aortic insufficiency is present. Other mediastinal conditions, as tumor or mediastinitis, may cause substernal pain. When such known pathological changes are present, the diagnosis should be that of the condition present, and treatment should be that which considers that condition.

Attacks of angina pectoris usually occur under conditions which entail additional work for the heart muscle. Exertion is the outstanding exciting cause. The amount of exertion is not constant for the individual and will vary in the presence of various physiological and psychological conditions. Attacks are most frequent after meals because of the increase in cardiac output at that time or this increase plus that produced by exertion or emotional excitement. Heavy or indigestible meals predispose to attacks.

The attack may follow any meal or it may be especially after breakfast in the morning when the blood pressure is lower, or after dinner at night when the heavier meal or the fatigue after a busy day may be an additional factor.

The attacks in some cases may come on only during the night and awaken the patient from a quiet sleep. Such attacks usually occur in the early morning hours when the blood pressure reaches its lowest level for the twenty-four hours.

In some patients the attacks may come on without apparent cause when the patient is resting quietly, but usually some relation to some exciting factor may be found.

A large nervous element in the precipitation of attacks has attracted attention since the time of Heberden, who classified angina pectoris with "the incubus, convulsive asthma, numbness, hypochondriac languors, and other ills justly attributed to the disturbed function of the nerves." In support of this he cited the "sudden manner of its coming on and going off, the long intervals of perfect ease," the "influence of passionate affections of the mind," and the number of years it will continue without otherwise "disordering the health."

The present-day observer cannot fail to be impressed, as Heberden was, with the importance of these causes of ner-

vous origin. His nomenclature may be different and he now recognizes that the factor of nervous or emotional origin produces its effects by means of physiological processes which increase the work which the heart must do in proportion to its blood supply or decrease the blood supply while the work which the heart is doing remains constant. Nevertheless, the importance of these causes remains.

Any of the emotions or mental excitement of any nature may precipitate an attack. Anger is a frequent cause. A patient may have frequent attacks on a day when the worry and strain of business life is increased, and few or none on a day when all is going well. Angina pectoris has frequently appeared in those previously free from attacks because of anxiety or of grief or worry over business reverses. Attacks may appear under emotional strain and disappear when the strain is removed. The same man who has daily attacks when he has the responsibility of an executive position to worry over may go on a vacation which calls for much more physical exertion than does his daily life at work and not have a single attack. Or the man who cannot walk from the station to his office without having to stop because of anginal pain, can play golf in comfort.

In these cases which show recurring attacks of anginal pain, the heart shows varying degrees of pathological change from a very great deal to those which are very slight or those which would be expected at the age. Between these two extremes is every possible gradation. In a portion of the cases the symptoms can very definitely be ascribed to pathological changes and in another part of the cases it is very difficult to ascribe the symptoms to pathological changes alone and some physiological factors must be considered. In a very small proportion of cases qualitative changes in the blood are a cause of anginal pain.

In part of the cases there are arteriosclerotic changes in the coronary arteries sufficient to interfere with the blood supply to the heart muscle. The blood supply may be sufficient for ordinary needs in the presence of these changes, or

for the needs of the heart muscle when the body is at rest. But when the heart muscle is called upon to do additional work, as during exertion or during nervous or emotional stress, or during the increased cardiac output occurring during digestion, the arteriosclerotic blood vessels are unable to meet the increased demands of the heart muscle for blood, and pain results. It is in such cases, also, with advanced vascular degeneration that attacks may come on during the night, in the early morning hours, during sleep, when the blood pressure is lowest.

Since the coronary flow is proportionate to the blood pressure, the higher blood pressure present during the day is able to maintain an adequate flow in spite of the vascular changes which are present. When the blood pressure falls during the night, the coronary flow, decreasing with the decreased blood pressure, becomes inadequate to compensate for the vascular changes. In those cases where attacks come on mostly in the morning, the lower blood pressure of the early morning is also a factor. The coronary flow is adequate when the patient is at rest, but not for the additional demands of exertion or those occurring during the digestion of breakfast.

In cases where there are vascular pathologic changes present in the coronaries not sufficient to cause symptoms under ordinary circumstances, a toxic thyroid, by its increased demands upon the work of the heart, may be the determining factor in producing attacks of angina pectoris. The increased emotional instability produced by this condition affords an additional factor.

Aortic insufficiency also furnishes an anatomical basis for anginal pain in some cases. The coronary flow varies with the blood pressure, but especially with the diastolic pressure. In aortic insufficiency, the low diastolic pressure may be such as to decrease the coronary flow to a point where it is insufficient for the work being done by the heart or insufficient in the presence of sclerosed arteries. The low diastolic flow is compensated for in part in most cases by an increased systolic pressure and to some extent by an increased heart



rate. These points must be kept in mind when treatment is planned.

Aortic stenosis is frequently accompanied by attacks of anginal pain. There is usually some degree of insufficiency present which in this case cannot be compensated for by a high systolic pressure or an increased pulse rate. In addition there is the increased work demanded of the hypertrophied left ventricle by the stenosis.

Old healed infarcts from a coronary thrombosis in which an adequate circulation has not been restored by anastomosis or collateral circulation may be the basis for recurring attacks or angina in some cases. In part of these cases we have a history of an initial attack of coronary thrombosis and in others a healed infarct may be found at autopsy which cannot be placed in the history.

Another anatomical basis for a decreased coronary flow is the partial occlusion of the mouth of one of the coronary arteries by changes in the aorta, especially changes due to syphilis. In a few cases there are congenital anomalies of the coronary arteries which may afford an adequate flow in early life, but a flow which becomes inadequate in the presence of the vascular changes which occur later in life.

It would appear certain that anatomical changes in the heart or its vessels constitute the chief basis of anginal attacks and play a part of varying importance in most of the cases. But such anatomical changes cannot be the sole factor. We still have to explain the attacks occurring in cases whose hearts are normal for their age. It is difficult also to explain the influence of the nervous and emotional background upon increased circulatory demands alone. Anatomical changes in the arteries do not explain why a man who has several attacks a day while at work has none upon a vacation where he is more active, but free from responsibility and worry, and why the attacks recur when he again returns to work. Certainly the vascular pathology does not change back and forth. There must be some other factor present. We cannot take the time to discuss this fully here, but it would seem to be connected

with an over-labile autonomic system. It is possible that it is a question of a generalized instability of the vasomotor system and an over-response to normal stimuli which throws an increased load upon the heart. It is possible also that a reflex vasoconstriction of the coronaries is responsible for the attacks in some cases or an increased tonus of the coronaries with inhibition or failure of the vasodilator response. Such a mechanism would not be normal and would not be to the biological advantage of the organism. The organism, however, is not living under conditions of life which are of biological advantage or it may not be a normal organism. The bronchoconstriction of asthma is not advantageous to the organism, but it does occur. In our animal ancestors one might feel that an autonomic system with a lowered threshold to stimuli and an over-response might have been of advantage under conditions of fatigue, but not with a response which involved a vasoconstriction of the coronaries. Such conditions, however, must involve the autonomic system as a whole and cannot be selective of any one function.

Whatever the mechanism, whether active changes in coronary caliber or some response which throws an increased load upon the heart, its association with an overlabile and over-active autonomic system would explain a great deal. It would help to explain the more frequent occurrence in the tense, nervous type of individual who has what Dr. Stuart Roberts very aptly terms the "spasmogenic aptitude." It would explain the more frequent occurrence of angina in business and professional men working under strain, and the effect of overwork, worry and fatigue with inadequate leisure, and inadequate or tiring vacations, for the autonomic system becomes more unstable with fatigue and with chronic fatigue or "staleness." It would explain the occurrence of anginal pain in the so-called "effort syndrome" for whatever that symptom complex is or is not, there is present a lowered threshold to autonomic stimuli and an over-response to those stimuli. It would explain the increased incidence of angina pectoris with

our changed social conditions, with lives of increased strain, and less real rest and relaxation.

Just how much of a factor tobacco is in producing attacks is uncertain. On the whole it probably has little influence. There are some cases which are associated with what is for the individual an overuse of tobacco. Smoking does have a vasoconstrictor effect upon the peripheral vessels and in experimental animals even very small doses of nicotine have a vasoconstrictor action upon the coronaries.

Digitalis administration is responsible for anginal pain under certain conditions in patients with a normal rhythm, and more rarely where more than the optimum dosage is given in auricular fibrillation. A decreased coronary flow has been observed when digitalis is administered to experimental animals. There are other variables determining the coronary flow volume, and while a decrease is observed more frequently than not, it does not always occur. It is assumed to be due to a coronary vasoconstrictor action of the digitalis. Increase in tonus of the heart muscle is probably not responsible for the decreased flow as the flow remains constant under changes in tonus produced in other ways.

In addition to a blood supply to the heart, which is quantitatively inadequate for the needs of the heart muscle, we find some cases where the attacks are consequent upon a blood supply that is qualitatively inadequate, or qualitatively inadequate in the presence of some degree of arteriosclerosis in the coronary vessels.

One such qualitative factor is the decreased oxygen carrying power of the blood in pernicious anemia. In the cases reported by Herrick, who first called our attention to anginal pain in pernicious anemia, arteriosclerotic changes were also present in the coronary arteries. The coronary changes are such as to allow an adequate supply of oxygen with blood of normal oxygen carrying power, but do not admit of sufficient oxygen in the presence of the impaired coronary circulation.

It is not only a question of sufficient oxygen supply. The heart muscle needs other materials carried by the blood, and

sugar is of especial importance. Cardiac pain due to hypoglycemia following the use of insulin has been discussed by several writers in recent years. Strouse and his associates have called our attention to anginal pain with a low blood sugar, following an inadequate carbohydrate diet. Sippe recently reported 4 such cases with a low blood sugar on their normal diet. Relief followed upon glucose given by mouth. Sippe also reported a case with a normal blood sugar, but a ketosis. Improvement followed upon an antiketogenic diet.

Anginal pain may also occur in cases with an abnormally high blood sugar but in whom a deficient insulin supply does not admit of its proper utilization. Such cases are relieved by the proper dosage of insulin.

While I have spent some time in going over the conditions which may constitute the basis for the recurring attacks of anginal pain, I have really gone over the ground much more hastily than I could wish. It is obvious that treatment is not the simple matter of prescribing some one remedy. Just what we are to do to help our patient will depend most of all upon a proper evaluation of the points which we have just considered as well as many other points which we have been forced to omit for lack of time.

The first requisite is that the physician himself should recognize that there is always something which he can do to help and that very often he can do a great deal. He cannot do it by writing out a routine prescription. The physician must obtain personally a careful history and be guided by what he learns from the history in each individual case. There can be no routine procedure. He must give time and thought and understanding and patience. No amount of careful "work-up" can replace the thoughtful understanding of one man who is in a position of leisurely and friendly contact with the patient and who is ready to assume responsibility for the future welfare of the patient.

A great deal of the patient's future depends upon what the physician says. A few years ago Rudyard Kipling in

addressing a medical audience spoke of the therapeutic value of words. And they have a great therapeutic value. In angina pectoris it is especially important just what you say to the patient and how you say it. There can be no fixed rule for this. Second only to the physician's knowledge of the science of medicine—in some cases even more important—is his ability to understand others, to appreciate what is going on in the patient's mind, to feel as he feels and to think as he thinks and to foresee the reaction to the spoken word. The physician must be able to "se fourrer dans la peau d'autrui"—to put himself into the other's skin. No matter what his anatomical background, the nervous element is always present in some degree and has as great an influence upon the patient's future welfare as it has had upon the genesis of his complaint. He must be given faith and confidence and encouragement, and at the same time be told enough so that he can best avoid attacks and prolong life. This is not an easy task.

It is rarely advisable to deny flatly to a patient that the pain of which he complains is anginal. There are some patients with whom such a flat denial is the wiser course and who are quite willing to assume that the pain is that of indigestion or of gas. If they will continue to think so, it is quite as well that they should, provided that the régime ordered by the physician is that which the actual condition requires and that they are kept under observation. But a great many of those who seek advice have had the doubtful advantage of our present-day popular education in medical matters. Daily perusals of health columns and other sources of information have already given them some idea as to what the basis may be. It is better to say what the pain is and to explain the condition in a way which gives them more confidence than to lose their confidence by a flat denial. To tell them that they must have and to have it in it, you must have it. It is impossible to discuss the condition frankly at the same time to ensure the patient's confidence and to help him to help himself. It is never better to say "certainly" than to say "no."

the patient's sake and also because you yourself do not always know sufficient in regard to the prognosis. Many a patient given a hopeless prognosis has been made infinitely worse by it and also many a patient given a hopeless prognosis is alive and well years afterward.

There will be a group of patients in whom there are symptoms other than the anginal pain, such as shortness of breath, dyspnea on exertion, and other subjective and objective evidences of impaired cardiac function. Part of this group will consist of those who have previously had a coronary thrombosis or in whom there is myocardial damage due to advanced coronary disease or other factors. Some of them may show very little in the way of objective findings and others will show definite findings of heart disease with or without congestive failure. Included in the group will be cases which show the resultant changes of rheumatic fever, of syphilis, or of renal disease. Here also will belong part of the cases of aortic insufficiency of either rheumatic or syphilitic origin. In all such cases, treatment must consider the pathological conditions present, their etiology, and just how they are interfering with normal physiological processes and functions. In a large part of this group, rest will be the first therapeutic indication, or at least some limitation of activity. It must be determined whether the infective process or other agent, as toxic thyroid, which caused the damage, is still active. If infection is still present or a toxic thyroid is active, that must be considered first of all.

In cases of syphilitic origin, it is best to proceed with considerable caution as regards treatment of the syphilis, and it is sometimes more prudent not to treat the syphilis at all. It is wise to bear in mind Dr. Hay's dictum and "treat the heart first, and not the syphilis." We will discuss this further when we are showing the cases.

There will be a large group of patients in whom the only subjective symptoms are the anginal attacks and in whom there are no characteristic objective findings. A part of this group may be found in perfect health aside from the anginal

attacks. In another there may be some slight evidence of impairment of cardiac function. In a portion of these patients some degree of rest may be advisable at the start. In some this may consist of complete bed rest with a gradual resumption of activity. This will have two objectives, to hasten recovery from fatigue and to permit possible recovery processes in the heart. In some a continued limitation of activity will be advisable. Just what to do in regard to rest is a matter of judgment in each case. There will be some cases where the apprehension caused by such measures will more than offset any possible good results.

Unless there are definite indications to the contrary, most patients are better if allowed to go about their duties and recreations about as usual with only moderate limitations. It is better from a psychological standpoint and there is the possibility also that with a moderate load put upon the heart, further anastomoses and collateral circulation may develop. In many cases the possible fall in blood pressure with prolonged rest is not to be desired. There are obviously patients who cannot be allowed to continue their duties, such as those whose duties would tend to precipitate attacks and those whose sudden incapacity would endanger themselves or others.

There is a great deal in the way of general directions for the patient which should be talked over with him in a quiet, friendly, unhurried and undisturbed visit. The possible exciting causes for attacks, and especially those applicable in his case, should be explained to him. As far as possible he should be instructed to avoid attacks, and to keep within the limits of the exertion which will bring on an attack. If an attack does come on, he should be instructed to stop and rest until it wears off. Unless the pain stops at once with the cessation of effort, he should take a nitroglycerin tablet. There is always the possibility that some recurring attack may be a coronary thrombosis. Because of this it is better that he should be advised that in the event of an attack which is more severe or which bears with it unusual symptoms, he should

return to his home at once in a manner entailing as little effort as possible, and advise his physician.

He should be instructed in regard to the necessity of leading a quiet, calm and orderly existence, avoiding strain and hurry and anxiety. He will find that he can cultivate a spirit of philosophic calm much more easily than he supposes. Shorter hours of work and more rest are always advisable. Recreation should be such as to afford rest and relaxation and such as does not add to the nervous strain. When possible a quiet, restful vacation is always a good start on the treatment and is a therapeutic measure which should be frequently repeated. Frequent quiet week-ends in some small-town hotel where he is not known and where he is out of reach of his business associates afford a very good rest. A short train ride to the hotel provides a sense of detachment from the worries of his daily life. He can take some books and loaf about his room, going to bed early and sleeping until he wakes up in the morning. The motor car is best left at home on the week-end rests and on vacations as well. It is much better to sit back in a comfortable Pullman seat and relax than to be under the constant tension of driving.

Rest before and after meals is an important part of the regimen. After breakfast he should rest before starting out on his daily duties. At noon he should rest before his lunch and after lunch as well. In the evening the patient should get home in time to become thoroughly rested before dinner and should rest after dinner for an hour or more. Fatigue interferes with digestion in adults as well as in children. After meals, during the period of digestion, the heart and circulatory system already have an additional load.

The diet should be adapted to the needs of the individual patient. It should be such as to be readily digestible and one which cannot cause gas. Full, heavy meals are to be avoided. In some patients hydrochloric acid with the meals is indicated and may help in preventing attacks.

There is no indication for any restriction of diet and certainly there is no need for restricting the protein intake, as is



occasionally done. It should not be below the daily protein needs. In the overobese an appropriate diet should be ordered. It is better if the diet is adjusted to the point so that it just about equals the patient's caloric needs. In some cases it may be better to prescribe small meals with the addition of something between meals, if necessary. The diet should afford a carbohydrate ratio sufficient to maintain the blood sugar at the higher limits of normal. If diabetes is present, it should be controlled without insulin in those cases where it is possible to do so and still maintain an adequate diet. In the cases where insulin is necessary, as it frequently is, the patient must adhere to a known and prescribed diet and to a prescribed insulin dosage. The insulin always should be such as to maintain the blood sugar at a level at which hypoglycemia can be certainly avoided. It is better to allow a trace of sugar to show in the urine.

Occasionally attacks of angina pectoris occur in those who are suffering from symptoms of duodenal ulcer. Some of these patients have an active ulcer with deformity of the bulb. Others do not show an actual deformity but show evidence of an overirritable bulb with frequently no ulcer. Such patients should be put under ulcer management and especially ulcer management associated with the use of some mild sedative as phenobarbital. In many of these cases the symptoms are only another expression of Dr. Roberts' "spasmogenic aptitude."

Many angina patients have a constipation of the spastic type. This should be controlled as far as possible by diet. A glass or two of hot water on arising may help. If necessary, liquid or solid vaseline or one of the preparations of vaseline which do not contain a cathartic can be used. Solid white vaseline is especially valuable. It is not hard to take. A large ball of it can be placed on the back of the tongue and swallowed night and morning. If the diet does not afford sufficient bulk, agar can be added.

If cathartics are necessary, the milder saline laxatives are

preferable. Strong or stimulating cathartics may predispose to attacks, especially in those patients with spastic colons.

The question of the use of liquor frequently arises. Some patients are unquestionably the better for its moderate use, especially the more elderly patients. Others with even a very moderate or small amount may have gastric disturbance which predisposes to an attack. Liquor is best avoided as a general rule.

Just what to decide in regard to the use of tobacco must be decided according to the individual patient. Its use should certainly be moderate and it should not be used on an empty stomach. If there is any question as to its harmful effects, it should be omitted.

Such general directions as have been indicated above are quite as important as any part of treatment. A little pocket booklet with some very sensible and wise general directions for the patient's use has been prepared by Dr. John Sproull of Haverhill, Massachusetts, and is a very good guide for the patient to have.

When possible, the patient should spend the winter in a warm equable climate. High altitudes are always to be avoided and especially so where there is much actual cardiac pathology. For every increment of elevation, the heart has just so much more work to do. Patients will frequently return from a vacation at a high altitude and inform you that your warnings in that regard were quite unnecessary, but others will return and tell you that they wish that they had obeyed your directions. The same caution applies in regard to trips by plane. Conditions may force the plane to remain at a high altitude for a long period. A trip from Omaha to Chicago at 6000 feet undid the results of months of care in the case of one patient.

The attacks themselves are best relieved by amyl nitrite or nitroglycerin. Amyl nitrite acts a little more promptly but is less convenient and always conspicuous, as well as being a source of annoyance to others. Nitroglycerin dissolved under the tongue acts promptly enough for all clinical pur-

poses. It is especially useful because it can be readily carried in the pocket or handbag and can be used without attracting attention at any time. It loses strength rapidly when exposed or with age; it is best purchased in the small hypodermic tube of 20 tablets and kept tightly stoppered. The usual dose is  $\frac{1}{100}$  grain. There are patients who have uncomfortable symptoms or very rarely syncope with this dose and in whom a smaller dose does better. The dose can be repeated if necessary. The other nitrites act too slowly to be of much use, although their action is more prolonged. If the attacks last long enough to demand a drug with more prolonged action, there are more serious aspects which must be considered.

Heberden recommended "spirituous liquors" in the treatment of the attack and they are still valuable. Hot, strong, black coffee is of help in some cases and may act as a substitute when other means are not available.

A large part of the treatment between the attacks consists of the evaluation by the physician of just what it is that predisposes to the attack and precipitates it, and the directions which the physician gives the patient as to his care. There is no remedy which will alter anatomical changes in the arteries and certainly none which will "cure" angina pectoris. Nor is there any one drug which will afford any degree of relief in all cases. But most cases can at least be materially helped by medication.

In our experience here we have obtained better results by the use of the purine base group than with any other one medical treatment. In some few cases almost complete relief has been obtained. In most cases some degree of relief has been obtained, from a very great deal to moderate or slight. As would be expected from the nature of the conditions which cause the pain in angina pectoris, there must be cases where relief cannot be obtained.

It is not possible to say which of the purine base preparations is the most valuable. On some occasions a result will be obtained with one preparation when another has not been

effective, or one will cause uncomfortable symptoms and another not. Of the theobromine preparations, we use most frequently theobromine calcium salicylate (theocalcine), or the alkaloid theobromine, and of the theophylline preparations, theophylline ethylene diamine (aminophylline) or theophylline calcium salicylate (phyllicin).

We make use of most of the other preparations at one time or another, however, partly because of their lower cost and partly because, for no reason which we can assign, occasionally one preparation seems to work better than another.

The alkaloid theobromine we prescribe in 5- and 7.5-grain tablets, and theobromine calcium salicylate (theocalcine) 7.5-grain tablets, one or two at a time. Theobromine sodium salicylate and theobromine sodium acetate we use in 10-grain capsules. The acetate salt carries a little more theobromine than does the salicylate. The dosage of the theophylline preparation is much lower in each case. The alkaloid theophylline is prescribed in 2-grain capsules, and the theophylline ethylene diamine (aminophylline) in 1.5-grain tablets, and the theophylline calcium salicylate (phyllicine) in 4-grain tablets.

All of the series have some disadvantage. Most of them may, and occasionally do, cause some unpleasant symptom in the way of nausea, gastric distress, headache, or nervousness. Theobromine calcium salicylate (theocalcine), because of its insolubility in the stomach, rarely causes unpleasant symptoms. The same is true of theophylline ethylene diamine (aminophylline). Theophylline calcium salicylate is equally effective and in some cases more so, and is usually well tolerated. All are best taken during the meal; a little food, then the drug and then the rest of the meal.

In experimental animals the theobromine preparations cause the greatest increase in coronary flow. The theophylline preparations are next, and caffeine the least effective. Theophylline ethylene diamine is quite as effective as a vasodilator of the coronaries as the theobromines because of the

vasodilator effect of ethylene diamine. The theophylline calcium salicylate is quite as effective clinically in our experience.

It is probable that some degree of tolerance is acquired of these drugs and Meyer has shown that not only tolerance is acquired, but a cross tolerance is acquired as well to others of the series. We have assumed that such a tolerance is acquired clinically and have thought on some occasions that we have had evidence of this in some of our patients. In order to avoid acquiring a tolerance, we have been in the habit of using the theobromine preparation one week and a theophylline preparation the alternate week. The effects of this procedure is open to question where cross tolerance is so easily acquired. With the same objective in mind, we have, where possible, used the medication for four days of each week and omitted medication for three days. While a tolerance may be acquired there are certainly a great many patients who do not acquire such a tolerance.

In the second case which we are to show this morning, theobromine preparations have been used steadily for seven years and for the past two years the patient has insisted upon using the alkaloid theobromine because she gets more relief with this preparation. If she omits the medicine, the symptoms return as before.

Another case returned for a check-up this week who has used the theobromine preparations steadily for eleven years and is still benefited.

In order not to discourage the patient by any untoward effects, at the onset, we start with the theobromine calcium salicylate (theocalcin) which only very rarely causes distress, and then alternate with the theophylline ethylene diamine (aminophylline) or the theophylline calcium salicylate (phyllicin). Later we try other preparations and use the preparation and dosage which we find the most effective and the best tolerated.

We think that in these patients who have shown little or no effect at first and then have done exceptionally well, there is an actual improvement in the underlying condition. This

has been the opinion, also, of Dr. F. M. Smith and he has confirmed this by his experimental work on the dog, showing that with the use of the purine base diuretics, there is an actual increase in the anastomoses and collateral circulation consequent upon the constant vasodilation produced by these drugs.

Good results have been reported from the use of various tissue extracts. In experimental animals when administered into the vein, they have been shown to increase the coronary flow, and to dilate the peripheral vessels. In the preparations which we have used, we have observed little or no increase in the coronary flow in the experimental animal.

In peripheral vascular disease the clinical results following the intramuscular injection of tissue extract have been definitely good, although there has been some doubt as to whether this clinical improvement was due to a vasodilatation or not. It is possible that the good results may be due to some factor other than vasodilatation and that they are concerned in some way with muscle metabolism.

In our experience with the use of tissue extracts, which has been relatively small, we have not found them as useful as agents of the purine base series, and we certainly do not feel that they could replace these drugs. In some cases we feel that they have been of very real value, and have caused further relief of symptoms when the purine base drugs were not wholly effective. In such cases we have continued the use of the purine base drugs. On a few occasions the patient has not done as well with their use, and we have considered that a fall in the systemic blood pressure was responsible for the result. Care must be taken not to inject into a vein.

Different nitrite preparations, especially those with a more prolonged action, as erythrol tetranitrite or sodium nitrate, may be used routinely to prevent the recurrence of attacks. In our experience they have been rarely necessary, but there are occasions when they should be given a trial. They should not be used to the point of maintaining a lowered blood pressure and in some cases we think that we have seen untoward

results from their daily and frequent use. The nitrite preparations are occasionally given to a patient in order to undertake some additional effort without an attack. We do not recommend this to our patients and prefer that they do not undertake the additional effort.

Alcohol taken wisely and moderately has a place in the treatment of angina pectoris in certain cases. "Wine and cordials taken at going to bed will prevent or weaken the night fits," wrote Heberden, and it is a method worth trying in some cases. Heberden goes on to state that "nothing does this as effectively as opiates" and they also must be considered today, and especially so when age or a degree of illness is reached when habit forming is not to be feared.

Phenobarbital is of great value, especially when used in conjunction with the purine base drugs, or with other medication. We prefer to use it separately and not combined with theobromine, in order that we may vary the dosage as necessary. We attempt to use a dose which will produce a sedative effect without drowsiness. Sometimes one of the more rapidly acting derivatives is of more value at night.

Potassium iodide is used a great deal as an orthodox method of treatment. I have never been able to persuade myself that I could attribute any favorable results to its use. It certainly will not bring about any anatomical changes in the vessels. But where a drug has been used so consistently for so long a period, one wonders if there is not some possible virtue in it after all.

Digitalis is best not used at all except in the cases where there are definite indications for its use, as auricular fibrillation or a passive congestion which does not yield to other measures. There is no reason in ordinary cases why it should be used, and there are reasons why it should not be. We have obtained definite experimental evidence that digitalis decreases the coronary flow and clinically attacks have been made more severe and more frequent by its use or have been precipitated by its use. Especially should it be avoided where there is an aortic insufficiency. In aortic insufficiency, the coronary flow

is at a great disadvantage because of the low diastolic pressure. In most cases this is compensated for in part by an increase in the systolic pressure and by an increased pulse rate. Digitalis may lower the systolic pressure, may decrease the pulse rate, and possibly further lower the diastolic pressure, each of which factors would tend to cause the coronary flow to become inadequate.

Those cases in which pernicious anemia is a factor influencing the attacks yield to proper treatment. If a hypoglycemia forms the basis for the attacks, diet or glucose by mouth should be sufficient.

Various surgical methods have been devised for the relief or prevention of anginal attacks. An adequate discussion would take more time than we can give here. The operations involving ganglionectomy or sympathectomy are applicable only in a few chosen cases and the results have not been encouraging. Paravertebral injection of alcohol into the first five thoracic ganglia, as advocated by White, is more effective and does not carry the mortality that the more extensive surgical procedures do. More recently Blumgart and his associates have advocated total thyriodectomy in the treatment of angina pectoris. Their results as observed over a period of two or three years have been satisfactory and our own very small series has shown good results; the cases must be chosen with great care and it is not a procedure to be used indiscriminately.

I have postponed showing cases until the last, and we shall be obliged to show them very briefly and give only the essential history and findings.

**Case 1.** This first patient is a white clerk, aged fifty-four, who entered St. Luke's Hospital in September, 1929 with typical attacks of anginal pain. These attacks came on while walking from his home to the elevated railroad and from the train to his work, and again on going home in the evening. He would have 1 or 2 attacks in the 4 blocks which would necessitate his stopping and sitting down. They would wear off in a minute or two and he would proceed. For several months the attacks would appear only once or twice a week, but for two weeks before entrance there were frequent daily attacks.

Physical examination revealed no evidence of cardiac pathology. A 2-meter chest plate showed a heart of normal contour whose transverse diameter was



43 per cent of the transverse diameter of the chest. The great vessels were normal. An electrocardiogram shows the T wave in lead II leading off from very slightly below the iso-electric line. Otherwise it was normal. Blood, blood chemistry, Wassermann and urine were normal. Blood pressure varied around 120 systolic and 80 diastolic.

The patient was discharged on the third day. He was instructed to take theocalcine, 7.5 grains four times a day for one week, and metaphyllin, 1.5 grains, each alternate week. There was no improvement and October 13, 1929 alkaloid theobromine, 7.5 grains, was substituted for the theocalcine, giving about twice the dosage of theobromine. November 11th the pains were some better, and definitely better on December 22nd. February 9th he reported that the attacks were "about gone" and were better in the week when he took the alkaloid theobromine. March 9th he reported that he had had no attacks during the preceding week. There was no pain until October when there was some slight pain, but not what he would call an attack. There was no pain until July 1, 1932 when he had some pain again. On both of these occasions no history of any provocative cause could be elicited. There have been no attacks since that time. Beginning in 1933 the medication has been taken only intermittently for a month or two at a time and a month without medication.

It does not seem probable that there was a coronary thrombosis at the onset. There was no history of an attack, but there was a history of isolated short attacks of anginal pain becoming more frequent. It is not probable that anastomoses and collateral circulation improved spontaneously in so short a time. We have, too, the definite statement that he was better the weeks that he was taking the more effective dose of theobromine, than when on the relatively smaller dose of metaphyllin.

We consider that in this case relief was obtained by the medication and that the long-continued medication and continuous vasodilatation increased the anastomosis and collateral circulation, resulting in the present complete relief from symptoms.

**Case II.**—This next case represents a very much less favorable type for treatment, but is a case which we are very sure has been benefited by treatment.

The patient is a housewife, aged sixty-two. She entered St. Luke's Hospital on April 18, 1928, complaining of dyspnea upon exertion and edema of the lower extremities which had been present for three years, and of attacks of anginal pain, present for the past two years. The attacks of angina pectoris occurred several times daily, especially after meals. There were also nocturnal attacks.

Except for the obvious evidence of aortic insufficiency, she is a normal appearing woman for her age and was not essentially different at her entrance seven years ago.

At the time of entrance, physical examination revealed a very typical aortic insufficiency with a loud diastolic and a loud systolic murmur over the aorta, and an associated mitral insufficiency. There was nothing in the previous history to indicate the occurrence of rheumatic fever or syphilis. There have been no pregnancies.

A 2-meter chest plate showed a left ventricular hypertrophy, the left border 11.7 cm. to the left, and the right border 3.1 cm. to the right of the mid-sternal line. The transverse diameter of the heart occupied 55 per cent of the transverse diameter of the chest. At the present it occupies 56 per cent of the transverse diameter of the chest. Repeated Wassermann and Kahn tests were negative at this time, and have continued negative. Blood chemistry was normal throughout. Routine blood examinations showed only a moderate secondary anemia. The urine was normal except for a trace of albumin. The electrocardiogram showed evidences of extensive coronary and myocardial changes.

The blood pressure on entrance was 310 systolic and 50 diastolic. It has continued high, and since leaving the hospital has varied from 300 to 198 systolic, and 56 to 44 diastolic. It has averaged high in January and less in July. It apparently bears no relation to the pain.

The patient remained in the hospital for two weeks. During this period of bed rest the evidences of passive congestion disappeared. The attacks of anginal pain were less frequent than when up and about, but the patient still continued to have several attacks daily. On discharge, she returned to the follow-up clinic, where she was placed upon the purine base diuretics at once with immediate improvement. She had less pain when up and about with this medication than when at rest without it. During the intervening seven years she has continued for the most part upon this medication. It has been discontinued several times for periods of two to four weeks. During these periods everything at all reasonable that we have heard of has been tried. Nothing was found which would give her as much relief as her regular treatment. During the last two years she has been upon the alkaloid theobromine and theophyllin ethylene diamine. Attacks still occur, but are less frequent and less severe. There will be periods of one to three weeks when there are no attacks, and at other times there will be 1 or 2 or 3 attacks a week. The last few months there has been less limitation of activity and fewer attacks than at any other time. Moderate shortness of breath still persists, but there is no edema.

During these seven years of observation it is possible that part of the improvement has been due to the increased anastomoses and increased collateral circulation which might have occurred spontaneously with time. The improvement, however, began at once with the administration of the purine base

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drugs. The symptoms even now recur with greater frequency and severity if the medication is discontinued. She is better also when upon the alkaloid theobromine than when trying the other preparations. We feel that the medication has played a part in producing the increase in the anastomoses and collateral circulation which has probably occurred.

**Case III.**—This especially healthy appearing man represents an unusually favorable type for thyroidectomy for the relief of anginal pain and has shown especially good results.

The patient is an electrician and the proprietor of a radio sales and repair shop, aged fifty-nine. He came to the out-patient department November 12, 1933, complaining of frequent attacks of anginal pain, loss of weight, and sleeplessness present since the previous June. The attacks of pain occurred frequently during the day on slight exertion, and at night while lying in bed he had as many as 12 attacks. He was unable to work and had been practically bedfast.

There was a very obvious toxic thyroid present, with a metabolic rate of plus 32. The blood pressure was 164 systolic and 90 diastolic with a pulse of 112. Although he improved during his preoperative course of iodine and there was an amelioration of his thyroid symptoms, there was no change in the frequency or the severity of his anginal attacks. Theobromine sodium acetate, 40 grains daily, showed no effect.

He entered the hospital on December 3, 1934 and a subtotal thyroidectomy was done the next day by Dr. S. W. McArthur. After an uneventful post-operative recovery, he was discharged on the eighth day.

He has had no attack at any time since the operation. The night before the operation he had several attacks of pain. Even changing his position or sitting up might bring on an attack. The night following his operation he got out of bed and closed the window and moved a screen without pain. It would seem that there was something else in addition to the lowered metabolic rate which was responsible for the absence of pain after thyroidectomy. It is very improbable that the rate was materially lowered in the few hours intervening between the operation and his undertaking exertion that he could not possibly have undertaken before the operation. On the ninth day after the operation the rate was plus 25.3, later falling to minus 25.6, where it still remained last month.

He regained his weight rapidly, passing his former weight, and returning to his usual weight when he resumed exercise. There have been no attacks between the time of operation and now. When I called him to ask him to come to the hospital, he had just returned from a 2-mile walk on a cold winter evening. There is no shortness of breath. He has even experimented with running.

This case has been, of course, an especially favorable case. The thyroidectomy would have had to be done, irrespective

of the angina pectoris. The case does not belong with the group which has been reported from Boston and which has shown such favorable results.

In showing this second case of thyroidectomy done for the relief of anginal pain, I do not wish to be understood as advocating this line of treatment except in a very few chosen cases. In the other case just shown, his condition quite aside from the angina indicated a thyroidectomy. In this case which we are about to show, every other possibility was exhausted before a thyroidectomy was done. Most cases can be handled medically and we think, as far as we know now, to better advantage. Until cases have been followed for a long period of time and the results watched carefully and impartially, nothing definite can be said as to the advantages of thyroidectomy in chosen cases of angina pectoris. It is obvious that no matter how satisfactory the results may be in some cases, the procedure will never be applicable to more than a well chosen few.

In this second case of thyroidectomy, the operation was only done after months of unsuccessful efforts with other treatment. We were especially hesitant because of the associated pathological conditions.

**Case IV.**—The patient is a normal appearing man of fifty-three, a real estate salesman. He entered St. Luke's Hospital in September, 1933 because of attacks of angina pectoris. Until two months before entrance the patient was in his usual health. About this time he began to have occasional attacks of anginal pain. These rather rapidly became more frequent and more severe until it became impossible for him to continue at work. Attacks are now precipitated by the slightest exertion so that he is practically bedfast. There are one to several attacks at night. There has been no shortness of breath but there is some mild substernal pain present between the attacks part of the time.

Physical examination showed nothing of great significance. The heart was within normal limits of size. There was a soft systolic murmur at the base, under the sternum, not transmitted. The heart sounds and rhythm were normal. Physical examination at present is quite unchanged except that he has gained weight and has not the nervous, apprehensive appearance which he had at that time.

Laboratory examinations showed the heart to occupy 47.7 per cent of the transverse diameter of the chest, 8.7 cm. to the left and 4.7 cm. to the right of the midline.

The electrocardiogram showed only moderate variation from normal between the attacks, but during the attacks the tracing showed a marked deviation from normal type, indicative of coronary involvement.

The blood pressure was 120 systolic and 74 diastolic on entrance, and has since varied only slightly above and below these levels.

The blood Wassermann and Kahn were strongly positive, and the spinal fluid Wassermann was mildly positive. There was a low paretic curve with the colloidal gold test. The basal metabolism rate was minus 12. Routine blood examination showed a moderate secondary anemia. The urine was normal upon examination and functional tests were normal.

The patient remained in the hospital for seventy-one days, and then was discharged to a convalescent home. During this time he received various theobromine and theophyllin preparations. Neither these drugs nor other attempts at medication showed any definite effect. He improved enough so that he could be up and around the ward, and while he was much better, still had daily attacks and occasionally attacks during the night. There was no improvement that could not be accounted for by bed rest and time.

We feel that in cases of syphilis involving the circulatory system we should be very careful in regard to our antisyphilitic treatment. What we do depends entirely upon the cardiac condition and treatment directed at the syphilis may be omitted altogether until the cardiac condition has improved. We are very certain that we have seen even mild cardiac conditions become rapidly very much worse with vigorous or even mild arsenical therapy. As Dr. William Allen Pusey puts it, "Syphilitic tissue is better than no tissue at all." There are doubtless cases where vigorous arsenical treatment does *not show untoward results, but we prefer not to take the risk.* We start with mercury or mercury and iodide, and with bismuth in alternate courses, and even watch these closely. If subjective symptoms are aggravated or the pulse rate is increased, we stop for a time.

*In this case symptoms became definitely more pronounced with mercury and with mercury and iodides or with bismuth, and all antisyphilitic treatment was discontinued temporarily.*

After discharge the patient continued to return to the outpatient department. Mercury or bismuth were again tried at various times for short intervals, but could not be continued steadily. The purine base drugs in one form or another were

continued. He felt that he was better upon the alkaloid theobromine and he received this most of the time.

In June, 1934, he was a little better clinically, but he still had several attacks daily and could not return to his usual occupations. The convalescent home could not keep him longer, and he could not take care of himself alone in a rooming house. It was decided to do a thyroidectomy in spite of the unfavorable outlook. He was accordingly operated upon June 30, 1934, by Dr. H. E. Mock, who did a subtotal thyroidectomy. He made an uneventful recovery and was discharged on the twelfth day. There were no anginal attacks after the operation during his stay in the hospital.

Since his discharge he has been free from his former attacks, except for a few scattered attacks on prolonged effort. He has some mild pain, described as a burning sensation, under the upper third of the sternum on walking. This may come on in two blocks or it may be only after seven or eight blocks and it goes away as soon as he stops.

He is taking the alkaloid theobromine and theophylline calcium salicylate on alternate weeks, as he states that he feels better on these two.

It is interesting that since the thyroidectomy the metabolic rate has been higher than before, and has varied between minus 6 and minus 8.

He is receiving alternate courses of mercury and bismuth in the skin clinic. At first these were discontinued occasionally because of some increase in the substernal pain, but now are going along continuously. Because of the spinal-fluid findings we do not wish to lose any more time than is necessary in our antisyphilitic treatment and will begin to use the arsenicals sooner than we otherwise would.

He is still limited in his activities, but has returned to work and to his normal mode of life. Even with the residual substernal pain, which was to be expected, he is infinitely better off than with the recurring and frequent attacks of angina.





## CLINIC OF DR. LOWELL D. SNORF

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

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### PAIN IN THE ABDOMEN: CLINICAL SIGNIFICANCE AND CONSIDERATION OF RELIEF

PAIN as a symptom of abdominal pathology is deserving of careful study since it is one of the most important single symptoms and often most dramatic to the patient. In consideration of this symptom we must use it in the broadest sense, varying from distress of mild character to that of a severe agonizing colic. This interpretation is obviously necessary since vague distress at times may develop into acute pain and also because it will necessarily vary with the individual reaction. Sensations of pain may be materially altered by the apprehensiveness of the individual. A practical analysis of pain should contemplate its origin and some rationale for its particular characteristics, some understanding of the pathologic physiology involved. One must consider, furthermore, whether the pain is intra-abdominal or extra-abdominal, as the symptoms may be very confusing.

In the interpretation of pain we must of necessity relate it to other associated symptoms. Seldom will it occur that a definite pattern of pain will be adequate in any instance to make a definite diagnosis.

Generally speaking, the walls of the abdominal cavity are innervated by the cerebrospinal nerves, while the viscera are innervated by the splanchnics. The lower surface of the diaphragm is supplied by the phrenic, the afferent nerves having their origin in the fourth cervical segment of the cord. The anterior and lateral walls of the abdomen are supplied by the lower six thoracic and first lumbar nerves. Pains originating in the stomach or other viscera may be referred to the surface

of the body supplied by the corresponding spinal segment. It is obvious, therefore, that diseases of the spinal cord may refer pain from these corresponding root segments which may simulate disease of the several viscera. Gastric and intestinal pains are thought to be due either to increased tension of the muscle wall, to involvement of the peritoneum or both.

Rapid distention of the stomach has been observed to produce pain, the intragastric pressure indicating that the muscular tension was the chief factor involved. The spasm of the pylorus is another example. There is a close relationship between hypersensitivity of the gastric nerves and pain as exhibited in the distress of ulcer of the stomach or duodenum. The absence of pain during observation of the large visible peristaltic waves strong enough to lift the abdominal wall or similarly noted during fluoroscopic study would indicate that the ordinary conception of increased muscular tone was not the prime factor causing the pain.

*A peculiar conditioning of nervous reflexes associated with an increased sensitivity of the nerves of the stomach or duodenum accounts best for the pain activated by the acid secretion.*

The mucous membrane of the stomach and intestines is relatively insensitive to thermic, tactile and chemical stimuli. When weak acid solution is put in the stomach bearing an active ulcer, pain will be produced and if, as Palmer has shown, the ulcer is quiescent, no pain will result. This would indicate that acid is an essential factor in the production of pain when proper conditioning of nerves occur.

It is more difficult, however, to produce pain in the intestines. Sudden distention of the colon from gas associated with excessive peristalsis or the injection of large quantities of water in the colon while in an irritable state, will often produce marked pain. These observations are essential to bear in mind when opportunity presents itself in test-out in the differential diagnosis between ulcer and disorders in the colon.

The peritoneum covering the stomach and intestine is also relatively insensitive, whereas the parietal peritoneum is very sensitive. It seems quite reasonable, therefore, that tension

on the parietal peritoneum from distention of the viscera produces much the greater part of pain. This is particularly true in perforations, local peritonitis and intestinal obstruction. The cramplike pain of intestinal obstruction seems to be due to the extreme tone initiated by excessive and vigorous peristalsis. When free portions of the intestine are involved, there is a tendency for the pain to be referred to the epigastrium or the neighborhood of the umbilicus, whereas that arising from fixed portions is usually related directly to the region involved. Let us now analyze the pain picture as it is related to various disorders in the abdomen.

A typical colic frequently means a definite pattern of pain or distress. We must also ascertain whether the pain is acute or chronic. An acute pain usually means sudden onset from infection, perforation, obstruction, or some intra-abdominal accident, as vascular occlusion.

Inquire as to associated temperature, shock, nausea, or vomiting. In the chronic recurrent pain picture is there relationship to food ingestion, either of quality or time, and does bowel movement or certain physical activity influence the pain? Whether acute or chronic we must attempt to determine the point of maximum intensity of pain; the direction and point of reference. Is it influenced by any test procedure and with what other symptoms does it occur?

Before discussing the intra-abdominal lesions, let us analyze briefly the pain as it may be referred to the abdomen from extra-abdominal sources.

Diaphragmatic pleurisy or pneumonia of the right lower lobe may produce a referred pain to the upper abdomen or even as low as McBurney's point. If jaundice is an accompanying symptom, as is not infrequently the case in pneumonia, the deception is complete. Only recently we observed a patient who had had a previous x-ray and diagnosis of cholelithiasis, who at the time was suffering from very severe upper right quadrant pain. Two days passed before there were sufficient physical signs in the lower right chest to bear out the diagnosis of pneumonia. The pain in the upper right

quadrant, although severe, was at no time associated with rigidity of the right rectus muscle and the temperature was out of proportion to the abdominal findings. Pneumonia was finally positively diagnosed.

Pulmonary tuberculosis or bronchiectasis may simulate a lesion of the abdomen. Tuberculosis particularly will be confused and rightly so, since it is not infrequent that we find intestinal tuberculosis following the pulmonary involvement, yet the involvement of the diaphragm, with pain referred to the neck through the phrenic nerve and a negative gastro-intestinal study, will make the diagnosis certain of uncomplicated pulmonary tuberculosis.

The abdominal nerves may be affected at their source, as in tabes dorsalis, osteo-arthritis, Pott's disease or osteomyelitis. When the bodies of the vertebrae are involved, it may require no little ingenuity to prove the origin of the pain. Pressure over the involved bone may reveal marked tenderness, as in Pott's disease or osteomyelitis. Bed rest and a body cast may be finally necessary to diagnose correctly the bone involvement.

A coronary accident may so closely simulate an intra-abdominal disorder as to lead to serious consequences. A brief case report of such an experience might be worth analyzing. A man, aged sixty-five years, came to the hospital complaining of severe right upper abdominal pain. He gave a history of similar attacks over a period of several years. As a rule, these attacks were sufficiently severe to require morphine for relief. At no time did this man note pain over the precordium, much less a reference pain into the left shoulder or left arm. He showed no particular evidence of shock; blood pressure was down to 100 systolic. Previous to my examination he had had a Graham-Cole test which failed to visualize the gallbladder. Diagnosis, therefore, of gallbladder disease seemed probable. However, when I was called to see him, it was quite evident that the man was having some distress related to the cardiovascular system. His chief complaint on the morning of my examination was that of dyspnea

and with continued observation it became apparent that the dyspnea was associated with Cheyne-Stokes respiration. The cardiogram was taken at once and revealed marked evidence of myocarditis and disturbance in the conduction time. He succumbed to this coronary accident, and postmortem revealed a large infarct in the myocardium. The gallbladder was normal. Evidences of numerous healed infarcts were found in the myocardium, probably accounting for the previous gallbladder-like colics that he had experienced before.

Experiences of this kind are quite common. Many physicians have noted similar confusion ever since Herrick called our attention to coronary occlusion in 1912, but one is never so impressed by the possibilities of confusion until he has made a number of mistakes. Recently a not dissimilar problem was presented. Acute pain in the abdomen was thought to be due to a perforated duodenal ulcer. The patient gave a history of a duodenal ulcer of many years' standing and had taken rather poor care of himself. Shortly before the onset of this acute attack of pain, he had noted definite recurrence of his ulcer symptoms. He experienced a sudden epigastric pain radiating slightly upward into the chest. This radiation, however, was rather diffuse and had none of the typical earmarks of cardiac accident. His temperature ran between 99° and 100° F., pulse slightly increased, blood pressure from 95 to 100 systolic, and no abnormal findings in the chest were noted. Because of the previous history and the present localized pain in the abdomen, it was thought he had a perforating ulcer of the forme fruste type and he was operated upon. No perforation was found, but the scar of the old duodenal ulcer was quite easily visualized. The following day definite evidences of pericarditis were noted. Recurrence of pain was also observed, and after several weeks the patient made a relatively uninterrupted recovery.

I think it is important that this mistake in diagnosis be commented upon inasmuch as the patient was subjected to a very serious surgical procedure that might have resulted in disaster. Following his operation a cardiogram was taken

and presented conclusive evidence that we were dealing with coronary occlusion. The mistake in the diagnosis might have been obviated had we taken a cardiogram prior to the operation. Frequently, of course, the cardiogram does not reveal any positive evidence within the first twenty-four hours and, therefore, in the presence of a negative cardiogram we must always be extremely cautious in the diagnosis of upper abdominal lesions in an individual whose age is compatible with coronary accident.

Pains from intra-abdominal lesions may best be discussed from the standpoint of the organs involved, especially when the pain pattern is fairly exact.

A typical attack of biliary colic is characterized by severe pain in the right upper quadrant of the abdomen radiating through to the back and usually to the right shoulder blade. The paroxysm usually begins and terminates abruptly. Very commonly there will be a residual soreness over the region of the gallbladder for several days. According to the criteria stated above, for the consideration of pain, we have here a definite point of maximum intensity under the right costal margin and radiation to the right shoulder blade. It cannot, however, be related to a definite physiologic functional disturbance since it seldom occurs regularly following meal taking. It is, however, often precipitated by an excessively heavy meal, particularly one containing fat. There is also associated symptoms of nausea, sometimes vomiting, and an increase in temperature. When jaundice occurs, the diagnosis is much more complete. This typical attack is usually connected with the passing of a gallstone. When obstruction of the cystic or common duct occurs associated with an active infection in the gallbladder, then the accompanying symptoms of shock, high fever and continued pain are evidences of *empyema* of the gallbladder. A sudden onset of pain with marked rigidity, evidences of shock and infection make the diagnosis more difficult because then perforated ulcer, acute hemorrhagic pancreatitis, coronary occlusion or mesenteric thrombosis must be considered.

Renal colic very frequently presents a typical picture. The colic may be due to kink of the ureter or the passage of a stone or of a stone blocking the kidney pelvis at the ureteropelvic junction. This colic is a paroxysm of pain noted in the flank and frequently radiating downward toward the bladder and into the thigh or into the testicle, penis or labia on the side involved. This pain traverses the field of distribution of the eleventh thoracic to second lumbar spinal segments. Burning and frequency of urination are quite constant. The finding of red cells in the urine is an added diagnostic point. We have observed that distention of the kidney pelvis by retrograde pyelography produces a typical colic. The hydronephrotic kidney of long standing causes little distress unless an obstruction of the ureter, as in Dietl's crisis, occurs. The pain from stone or kinking of the ureter is due undoubtedly to an increased tone and distention of the kidney pelvis or of the ureter itself rather than to direct irritation from the stone on the mucosa. Less typical attacks of pain occur from disturbance of the kidney and require a great deal of care in the differentiation from the more chronic type of distress produced by the colon or by recurrent appendiceal infection.

A woman, thirty-two years of age, complained of pain in the right lower quadrant in the region of McBurney's point for several years. Because of this constant annoying pain and the associated disorder of the colon function, the appendix was removed. The distress originally complained of continued. There was never any sign of acute colic, no frequency or urgency of urination, and no abnormal urine findings; at the time of our examination it was noted that the kidney was easily movable and when placed upon her left side the kidney traveled out to the region of the umbilicus. She was then examined while in the upright position. The kidney was found to be at the level of the crest of the ilium and when pulled downward it was possible to reproduce the pain which she had previously experienced. On advice her kidney was studied both by intravenous urography and retrograde pyelography. A marked ptosis with definite hydronephrosis and associated ureteral angulation were found. Proper measures were instituted and the pain disappeared at once.

I am quite convinced that every patient with chronic recurrent right-sided pain should be studied from the stand-



point of possible kidney involvement. Undoubtedly strictures of the ureter will produce such symptoms.

An uncomplicated peptic ulcer usually produces a typical pain pattern. Here it is extremely important to study the type of pain with relation to the several criteria noted above because in so doing we are able to evaluate to a great extent the nature of the lesion and something of the progressive pathology if and when such changes occur. Distress of ulcer, as we are all quite familiar, may be no more than fulness or present the severe agonizing pain associated with acute spasm or perforation. The pain of uncomplicated ulcer, whether gastric or duodenal, is usually noted in the midepigastrium. It seldom appears in the morning before breakfast, usually occurs an hour or two after meals and occasionally it noted at twelve to two o'clock in the morning. It regularly is relieved by adequate alkali, food, vomiting and aspiration.

When the ulcer becomes complicated by obstruction, perigastritis or perforation, the pain then may vary considerably. In the presence of obstruction it will frequently continue until the next meal. When it is associated with obstruction due to spasm, the pain frequently will be quite intense, but will still be relieved by food and alkali. When obstruction is associated with definite cicatrix formation, a continued secretion is likely to be present and food and alkali may not give such complete relief. Aspiration or vomiting, however, invariably give prompt and complete relief. Perigastritis, or periduodenitis, indicates an inflammation of the peritoneum and here the pain is not always completely relieved by food and alkali; in fact, sometimes it is aggravated. Furthermore, the pain is likely to be accentuated by change of position and also by increased peristalsis.

It is well to remember particularly this fact, that pain of an uncomplicated ulcer, whatever its cause, will be relieved by food, alkali, vomiting and aspiration. If we will use this as a simple procedure for test-out observations, we will usually be able to differentiate very satisfactorily between gallbladder disease and peptic ulcer. The following case report will sug-

gest the varying pathology in ulcer as indicated by the changing pain picture.

A man, aged forty, came to the hospital seeking treatment for "ulcer of the stomach." He stated that he had had symptoms of stomach trouble during most of his adult life. As a young man he had what was called heart burn, occurring several days in succession, always appearing an hour or more after meals and relieved by soda. For this his appendix was removed. Within a few months he had a recurrence of distress that had more the nature of definite pain. This also was present an hour or more after meals. Periods of relief followed by periods of definite pain continued for more than ten years. The pain at first was relieved by food and soda and seldom appeared at night time. Later on, however, the pain was not so completely relieved by the average dose of soda. He was awakened frequently at night time and finally, on occasion, would vomit a large quantity of fluid out of proportion to the amount that he had taken. Vomiting would give complete relief of distress. One night he was suddenly seized with severe pain in his upper abdomen requiring the services of a physician who gave him morphine for relief. He states that the abdomen was extremely sore and tender for several weeks after this attack. He was forced to remain in bed because of the severity of the symptoms for more than a month. Some months after this particular incident he had a recurrence of symptoms similar to those experienced before the abdominal accident. He then for the first time in this long experience of gastric invalidism was given the advantage of an x-ray study. It was found that he had a duodenal ulcer. He was operated upon and a gastro-enterostomy performed. The surgeon stated that the duodenum was immobile, being fixed to the surrounding viscera by dense, thick adhesions. His recovery from the immediate effects of the operation was uneventful. Some weeks later he experienced pains in his abdomen located to the left of the midline. This pain, when it occurred, would radiate downward to the groin. Occasionally he would vomit. He obtained relief from the distress by vomiting and by the taking of alkali. In fact, he obtained complete relief for a time on a carefully supervised diet. Subsequent examination of the gastro-intestinal tract revealed the stomach emptying through the gastro-enterostomy stoma and evidence of spasm in the stoma with distinct pain over this area. He was operated upon again and a jejunal ulcer resected.

Study of this patient reveals variations in the character of the pain based upon the changes in the pathology that developed from time to time. At first the pain and distress were that of an uncomplicated ulcer. Later the pain picture changed with the presence of obstruction. Later still the acute attack of pain was definitely that of a perforating ulcer of the duodenum and finally the pain produced by the complication from the perforating jejunal ulcer. When the pain of

ulcer shifts in its position from the midline to the left, one is usually dealing with a penetrating gastric ulcer or, more likely still, a jejunal ulcer. We have noted, as have others, that pain of a penetrating or perforating jejunal ulcer frequently radiates downward to the groin and, as Dr. Ralph Brown reported, actual radiation into the left testicle. When pain is felt in the back, it usually means that the simple ulcer has become complicated by perigastric or periduodenal adhesions or that there has occurred a forme fruste type of perforation. Relatively acute pain recurring regularly day after day usually means spasm of the pylorus, while gradual decreasing severity of pain over a period of years suggests a scarring of the ulcer area. There is definite prognostic value in the proper and careful study of pain.

Abdominal pain is one of the commonest complaints, often the chief symptom, of the gynecological patient. It is usually low on one or both sides, less likely in the midline and seldom above the umbilicus. Pain of tubal and ovarian lesions is noted regularly over the brim of the pelvis and frequently on the corresponding side of the diseased organ. It is frequently precipitated by the onset of the menstrual flow. Repeated torsion of small ovarian cysts may frequently account for recurrent low abdominal pain. When the pain is generalized over the lower abdomen, it suggests the possibility of tuberculous peritonitis. Ectopic pregnancy and pyosalpinx are frequently confused with appendicitis. A pelvic examination may be the only means of definitely differentiating the conditions. On the other hand, sigmoid spasm, if prolonged and if of unusual severity, may be extremely confusing.

Appendicitis is invariably associated with some degree of pain. We are accustomed to accept the diagnosis of appendicitis on the basis of generalized abdominal pain, perhaps accentuation in the epigastrium and then gradually localizing in the region of McBurney's point with an associated local rigidity. The pain may be extremely severe, although as a rule it is accentuated chiefly by pressure directly over the cecum. The appendix alone is involved when the pain

is referred to the epigastric or umbilical region and later on involves the parietal peritoneum when the symptoms localize in the right lower quadrant. The pain of acute appendicitis may be confused with gallbladder or kidney disease, especially when the organ is located retroceally. Likewise, it may be confused with disease of the ovary or tube and particularly in older individuals difficult to differentiate from diverticulitis. When the pain is less severe or when it is associated with disturbances of the colon, particularly with the irritable bowel dysfunction, diagnosis may be very difficult indeed and it becomes obvious that the associated signs and symptoms of appendicitis must be taken into account rather than relying entirely upon the pain picture.

The irritable and spastic colon may produce pain which will mimic the pain of peptic ulcer, gallbladder colic, appendicitis, intestinal obstruction, or pelvic disorders. The pain usually shifts from one section of the abdomen to the other, may be aggravated by food ingestion, cold drink, chilling the surface of the body and often precede a bowel movement. It is induced by or aggravated temporarily by a large water enema. Coarse foods usually offend it. It may be associated with extra-gastro-intestinal pathology, as in thyrotoxicosis and Addison's disease. It is frequently influenced by infection of the gallbladder, appendix, and by irritating lesions about the rectum and anus. It may be confused with lead poisoning, diverticulitis and postoperative adhesions. The possibility of an allergic state must be always borne in mind.

The colon is frequently palpable throughout its entire course and the patient is often quite conscious of the segments involved. The pain may subside and be followed by a sensitiveness and unrest comparable to pain, but of a less severe degree. In long continued irritabilities with or without ulcerations or inflammations there is frequently an associated psychic disturbance which requires the most careful evaluation in order to obtain a successful cure. The more often we meet these particular intestinal invalids, the more we appreciate the factor of mental instability as one most necessary

to treat. Mucous colitis, although manifesting primarily a colon disorder, is invariably associated with a definite nervous makeup. The pain associated with expulsion of mucus is, I think, no different than spasm of the colon in the non-inflammatory colon, and mucous colitis is in reality a highly irritable colon with excess mucous secretion in a highly nervous individual. This conception is essential to a full understanding of the treatment of pain later described.

The control and relief of abdominal pain presupposes not only an accurate diagnosis, but a full appreciation of the structural and functional changes involved.

Since the pain is so important as a diagnostic sign, balanced judgment must at all times be exhibited whenever medication is to be instituted. No treatment for relief of pain must ever be permitted until the diagnosis has been made or at least until it seems reasonably certain that either the further study of the pain symptoms is unimportant or that the emergency demands immediate relief. This particularly pertains to the acute abdomen. The treatment of any symptom is, perforce, secondary to the contemplated treatment as a whole; nevertheless, pain as such is so important to the patient that definite measures must be instituted for its control.

Severe colic or pain of sudden onset is best relieved by  $\frac{1}{4}$  grain of morphine given hypodermically. If this does not alleviate the pain, it should be repeated within a half hour. In acute pancreatitis or ruptured peptic ulcer, there is evidence of a definite emergency and since surgery is necessary, scopolamin  $\frac{1}{150}$  grain may be added as it not only aids in relieving the mental anxiety, but prepares the patient for the subsequent anesthesia. If a gallstone colic or renal colic is diagnosed and no vomiting is present,  $\frac{1}{4}$  grain of morphine sulphate or  $\frac{1}{2}$  grain of codeine phosphate may be given by mouth. This is perhaps only justified if the patient is unduly apprehensive about a hypodermic.

Pain from appendicitis seldom requires a sedative and if it is severe enough, should then only be relieved when operation has been definitely decided upon. Pain due to torsion of

an ovarian cyst or fibroid on its pedicle or due to ruptured ectopic pregnancy requires morphine as early as feasible.

In general, when a diagnosis of an abdominal accident is made surgery, when not contraindicated, should be instituted as soon as possible. When that decision has been arrived at morphine, pantopon or codein should be used to relieve the patient of all the suffering possible. One need not fear any harmful effect on the subsequent anesthesia.

In general or local peritonitis, where for some reason immediate operation is not deemed advisable, morphine should be used freely. Since the pain is frequently the sign of intestinal activity, it may remain as a guide of therapy. Peristalsis should be kept at a minimum of activity. In local peritonitis, as found in diverticulitis, milder sedatives may be used, especially when the sigmoid is involved.

The postoperative "gas" pains should, I believe, be treated more conservatively than is the usual practice. This scarcely requires consideration within the scope of this paper, but perhaps these few comments are in order. It is true that at times such vigorous enemas as milk and molasses or the commonly used 1-2-3 enema may give good results by producing peristalsis and the subsequent expelling of gas. These pains are usually due to lack of peristalsis and distention of loops of intestine. This dysfunction disappears within a few days after the normal tone and function have returned. Continued injections of various irritating fluids can certainly result in prolonged gas pain disturbances or worse still an aftermath of colon irritation which the patient will carry for a long time. It has been my experience that a rectal tube, an opiate, pituitrin, or prostigmin along with heat to the abdomen, when acceptable, will do as much or more good than laxatives and enemas and be followed by less intestinal invalidism later.

The management of the more chronic and recurrent abdominal distresses and pains requires the consideration of several therapeutic measures; namely, drugs for sedative and antispasmodic effect, diet, physiotherapy, and psychotherapy. These four measures are involved in varying degrees in the

proper and successful handling of peptic ulcer, irritable colon, chronic constipation, ptosis of the kidney and the other disorders mentioned.

In simple uncomplicated peptic ulcer pain is almost invariably relieved by adequate alkali and food. By adequate alkali is meant sufficient amount to neutralize completely the acid gastric juice. A powder containing sodium bicarbonate 30 grains and calcium carbonate 30 grains taken in  $\frac{1}{2}$  glass of water will produce relief within five to ten minutes. One glass of milk and a few crackers will produce the same results. However, if the ulcer is in a fairly active state, the pain will recur after a time or usually again after a later meal and, therefore, the powder must be repeated. This procedure will not be effective as a management nor should it be continued as such since the patient will not be cured, but will be lulled into a state of false security. The control of the pain of peptic ulcer will be incorporated in the general management. In a properly managed ulcer diet the pain usually disappears within a day and seldom is it noted after the third day. In fact, when present after six to eight days, some complication should be suspected and searched for. When night pain is noted, alkalis should be given every hour or two throughout the night. This pain indicates obstruction at the outlet with an associated continued secretion. This latter complication will best be controlled by emptying the stomach with a tube at 10 P. M. and 1 or 2 A. M. Frequently pain that persists at night will be promptly relieved by instituting this procedure for three or four successive nights. Coarse and irritating foods frequently precipitate trouble and, therefore, should be avoided.

Other drugs than alkalis are seldom needed for control of pain. Occasionally tincture of belladonna in 10-minim doses three times daily is used. More often a sedative of 10 grains of sodium bromide given three times daily or a barbiturate will help control the apprehensive patient. Papaverin hydrochloride  $\frac{1}{4}$  grain, elixir phenobarbital  $\frac{1}{4}$  drachm taken three to four times daily will be effective.

I have never been convinced that atropine in safe doses could be used long enough to demonstrate any great clinical benefit.

In the forme fruste type of perforation, where operation is not considered, the above-mentioned medications are used and in addition hot wet packs to the abdomen are effective. Aside from alkali no part of the management of ulcer is so essential and withal as poorly appreciated as rest and relaxation. If this could be definitely made a part of the management of all early ulcers, less ulcer invalids would develop.

The pain and distress of an irritable colon are due to a disorganized functioning of that organ. Varying states of tension and spasm in the musculature are present with resulting colic, pain, soreness and unrest. These subjective symptoms are best managed by such measures as will allay peristaltic unrest and tend to develop an orderly functioning of the colon.

For the acutely persistent pain or spasmodic colic, the patient is placed at absolute rest and heat is applied to the abdomen in the form of hot wet packs, hot water bags or electric pads. Tincture of opium 5 minims or camphorated tincture of opium 30 minims are given especially if there is an associated diarrhea. Codein or morphine are seldom necessary and then not to be given without the greatest certainty of diagnosis. Cathartics should never be given. The diet should consist of low cellulose residue as warm or boiled milk, soft eggs, toast and cooked cereals. As the colon becomes quiet, cooked fruits and cooked vegetables (all strained) may be given in increasing amounts until a normal diet is attained. This may require days or weeks of diet restriction and of careful food selection. Ice cold drinks, excessive fruit juices, bran, beer and buttermilk and specific foods to which the patient knows he is sensitive should be avoided. In the less severe pain the same dietary scheme should be used. Tincture of belladonna 10 minims and sodium bromide 10 grains, each three times daily after meals, will usually quiet the pains of flatulence and peristaltic activity. At times atropine  $\frac{1}{150}$



to  $\frac{1}{75}$  grain repeated four times daily will be more effective. If continued over any great length of time it may be found necessary to increase the dose. Syntropan has recently been advocated as an excellent antispasmodic.

The management of the type designated as mucous colitis is for all practical purposes the same. It seems scarcely ever necessary to resort to colonic irrigations or large water flushings either for treatment or the control of symptoms of either the ulcerative, noninflammatory or functional disorders of the colon. Should impactions develop due to improper management, enemas will be necessary for temporary relief, but this complicating trouble is obviated by the use of 2 to 3 ounces of warm olive or cottonseed oil as a retention enema when the bowel fails to move or the movement is hard and dry.

No specific dietary measures are to be followed for relief of pain as such in the treatment of disorders of the gallbladder, kidney or appendix or the several other conditions mentioned before.

Physiotherapy is considered frequently in management of the various chronic disorders of the abdomen not only as to treatment, but especially in the control of pain. The management of pain under consideration seldom requires infra-red or ultraviolet radiation and I have been so regularly disappointed in diathermy as a therapeutic agent in disorders of the colon as to abandon its consideration entirely.

Ice-bags to the abdomen in acute appendicitis remain in favor largely because presumably it is thought to limit the progress of the pathological process and also since it does seem to relieve pain. Heat to the abdomen will relieve pain in this disease, but is not to be recommended. Cold packs do not seem to be effective in any of the other disorders here considered.

Heat in the form of hot wet packs, hot baths, or electric pads comes nearer being the most specific physiotherapeutic measure available.

Hot wet packs should be applied continuously in local peritonitis of pelvic origin or in acute diverticulitis. Pain is

often readily controlled. They should be used in perigastitis and where spasm and pain of ulcer are difficult to control. A hot tub bath of five to ten minutes' duration may be resorted to in the presence of kidney or gallbladder colic or severe spasm of the colon. The hot-water bag or electric pad is regularly used for the acute colics, but especially in the more chronic recurrent pains of the colon. In the latter condition heat is applied one-half to one hour with a discontinuance for a like period of time, but to be continued for a longer time than the duration of the distress. Heat to the abdomen in the chronic intestinal invalid offers to that patient the greatest solace.

Massage is seldom to be recommended, although occasionally very light stroking over the colon by the experienced hand seems to be effective. Certainly deep, vigorous massage will aggravate rather than lessen the pain of colon origin. It should not be recommended in any other condition. I have suspected that the good noted by the patient has been largely psychic.

Pain from ptosis of the kidney or, as occasionally occurs, from ptosis of the stomach with an associated duodenal angulation will be relieved often by the wearing of a properly fitted supportive belt or corset. Special pads, cushions and straps seem to lend little more to the effectiveness of the corset than can be expected to come from the general support and relief from the tension on the attachments of the various organs.

The successful physician succeeds best who practices, knowingly or unknowingly, some measure of psychotherapy. The soothing influence from the comforting physician is never to be forgotten as one of the most effective therapeutic measures and pain in most instances is markedly increased by the fears of uncertainty. If the origin of pain can be definitely ascertained and proper measures of control instituted, a great part of the battle is won.



## CLINIC OF DR. J. P. GREENHILL

### COOK COUNTY HOSPITAL

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#### RELIEF OF PAIN ARISING IN THE FEMALE PELVIS

PATIENTS are more grateful for the relief from severe pain than for anything else which physicians can do for them. Fortunately in most instances, the cause of excruciating pain can be determined and removed. Thus, for example, the severe pain due to appendicitis, ruptured ectopic pregnancy, ruptured hollow viscus, etc., may be relieved by surgical operations. In other instances, excruciating pain can be relieved by the opiates as in cases of gallbladder colic, renal colic, etc. However, there are many instances where the source of annoying pain cannot be found or, if determined, it cannot be removed or satisfactorily relieved.

In the female pelvis the genital organs are a frequent source of severe pain. In inflammatory diseases of the tubes and ovaries, especially those due to gonorrhea, the pain may usually be relieved by conservative treatment. However, in many instances an operation is necessary to bring about relief. Following such operations, most of the pain disappears. Less frequent causes of pain in the pelvis are fibroids which produce pain by pressure on other organs or submucous fibroids which the uterus attempts to expel.

Endometriosis is another pelvic condition which usually produces pain. The pain associated with this abnormality as well as that due to fibroids may be relieved by surgical measures and sometimes by radiation therapy. Ovarian tumors occasionally cause pain and this pain may also be eliminated by removal of the growths.

There are, however, types of pain in the pelvis which are difficult to relieve. These are the severe dysmenorrheas, the

intractable pain associated with carcinoma of the cervix and other pelvic organs, and pain which occasionally follows operations in the pelvis and lower abdomen.

**Dysmenorrhea.**—Dysmenorrhea is generally divided into two types, primary and secondary. The latter is caused by pathologic conditions in the pelvis, usually uterine fibroids, endometriosis, or salpingitis. Surgical correction of the pathologic disturbance usually cures the menstrual pains. Primary dysmenorrhea, on the other hand, is not associated with any abnormality in the pelvis and its treatment is one of the most baffling problems with which physicians have to deal. Almost every type of analgesic drug has been employed to relieve primary dysmenorrhea, but not one has given any semblance of uniform success. There is no unity of opinion concerning the exact cause of this type of pain. Novak and Reynolds are of the opinion that the immediate cause of dysmenorrhea is an exaggerated contractility of the uterus, manifested by pain if the pain threshold is lowered or if there is an actual imbalance between the two hormones that appear to regulate this. These two hormones are the follicular factor, the normal stimulant of uterine excitability and progesterin, the normal inhibitor. Hence, Novak says in cases of dysmenorrhea it is advisable to administer biologic uterine antispasmodics and the one recommended is the luteinizing principle obtained from the urine of pregnant women. Other individuals believe that the strong pains associated with menstruation are due to an imbalance in the pelvic sympathetic system. Perhaps both factors are involved.

Because the exact etiology of dysmenorrhea is still unsettled, treatment is in most cases empiric and not satisfactory. There are a large number of young women who suffer inexorably every month in spite of what is prescribed. For those who are not helped by medication, physiotherapy, psychotherapy, dilatation and curettement and other measures, resection of the superior hypogastric plexus yields excellent results because in the large majority of cases instant relief is obtained. This operation will be described shortly.

**Pain Due to Pelvic Malignancy.**—Carcinoma of the uterine cervix is one of the most serious afflictions a woman can develop because at least three out of every four women who have the disease die from it. Furthermore, nearly all of these women suffer excruciating pain during the latter part of their lives and in a large proportion of cases the pain is constantly present both day and night and is almost unbearable. This is due to the fact that the sensory nerves become involved in the malignant growth. There are at present three means of relieving this pain. The first and the one almost exclusively used at present is the administration of derivatives of opium, chiefly morphine. However, there are disadvantages to this form of therapy, particularly the necessity of giving constantly increasing doses as the patient's tolerance increases, the nausea and vomiting which some women experience, the idiosyncrasy of others, the addiction which many women develop, the excitement produced in some and the expense for poor patients. The second method of giving relief from pain is surgical and consists essentially of pelvic sympathectomy and chordotomy. The third means of relieving pain consists of blocking the nerves which conduct pain sensation. This may be accomplished by a number of different solutions, but alcohol is the most commonly used.

**Intraspinal Alcohol Injections.**—The simplest of the aforementioned methods is the intraspinal (subarachnoid) injection of absolute or 95 per cent alcohol. It is based upon the idea of destroying some of the nerve fibers in the posterior nerve roots, these being the roots which convey the sensation of pain. Injection of absolute or 95 per cent alcohol into the subarachnoid space will prevent all painful peripheral stimuli from reaching the medullary centers, even if the stimuli act at the level of the spinal ganglia, the intervertebral foramina or the spinal roots. The technic of the injection is as follows: No preliminary medication is given because we wish to observe the immediate effects of the injection. Most patients with advanced carcinoma of the cervix and other genital organs have much more pain on one side than on the other. The

patient is placed on the side opposite to that where most of the pain is present. A pillow or pad is placed under the pelvis and side to elevate the sacral and lumbar portions of the spine, her back is arched as much as possible, her body turned somewhat ventrally and the head lowered slightly. By placing the patient in this attitude we raise the sacrolumbar region of the spine to the highest level and at the same time make the posterior or sensory nerve roots lie horizontally. The anterior or motor nerve roots come to lie in a plane which is usually out of reach of the alcohol. Even if the motor nerves are not removed from the field of the alcohol, they are not often affected because sensory nerves are more susceptible than motor fibers to the effects of alcohol.

Someone should hold the patient in the proper position. A weak solution of iodine or other antiseptic is applied over the lumbar and upper sacral regions. In most of my cases the fourth lumbar interspace is selected for the injection of alcohol and the results have been highly satisfactory. An ordinary lumbar puncture needle with a stylet is used. The needle is injected into the desired interspace just as for an ordinary lumbar puncture and I prefer not to use novocain in the skin before inserting the needle. After the needle is in the subarachnoid space, as evidenced by the flow of spinal fluid, 0.5 cc. of absolute or 95 per cent alcohol is injected into the cerebrospinal fluid. For this purpose it is best to use a tuberculin syringe so as to be sure not more than 0.5 cc. is injected. Furthermore, the alcohol must be injected very slowly, drop by drop, taking about two minutes for the injection of the 0.5 cc. This will avoid a mixture of the alcohol with the spinal fluid. The alcohol rises immediately to surround the posterior roots because the specific gravity of alcohol is about 0.806, whereas, that of the spinal fluid is 1.007. No attempt should be made to draw spinal fluid into the syringe to mix it with the alcohol because this is exactly what is *not* wanted. After the injection is made the needle is withdrawn and the puncture hole covered with sterile gauze and adhesive. Before the injection is completed, the patient will complain that the

upper leg feels numb or hot and that she cannot move the leg. The numbness is almost routinely experienced after the injection, but disappears spontaneously after a few hours or few days in most of the cases. In spite of what the patient says concerning her inability to move the leg, she can easily move it when requested to do so. At the same time that the patient informs us of the numbness she also often tells us either voluntarily or in answer to our query that her pain has disappeared. The longer the patient is permitted to lie on her side, the better the results. Hence I now keep my patients on their side for two hours after the injection. Then these women are permitted to get up and walk around. Some find difficulty in getting up from a chair because their "leg is asleep." Sometimes the leg feels heavy and the patient experiences some trouble in walking up steps because the knee flexes readily. These sensations usually wear off in a few hours, although in some women they last a number of weeks. Nearly all of my patients went home within three hours after the injection and no ill effects have been observed from this procedure. It is perhaps best, however, to keep the patient in a hospital for at least twenty-four hours.

If the patient has pain on both sides, an injection is made a week later with the patient lying on the opposite side. The same amount of alcohol is injected.

Formerly I restricted the subarachnoid injection of alcohol to patients with hopelessly advanced cancer. Until we knew more about the effects of absolute and 95 per cent alcohol on the spinal cord I did not extend the use of this procedure to other cases. Recently we have obtained striking results in cases of pruritus vulvae.

Thus far my associate, Dr. Herbert E. Schmitz, and I have performed alcohol injections on 45 women who have advanced cancer of the cervix. We have completely or greatly relieved all but four of these patients. Some of these women have been free from pain for as long as ten months. A few who had pain on both sides and who experienced almost immediate relief on



one side after an injection, asked that the injection be repeated on the other side.

**Pelvic Sympathectomy.**—Another procedure which has yielded excellent results in cases of hopelessly advanced cancer of the genitalia is the operation known as pelvic sympathectomy, resection of the presacral nerve or resection of the superior hypogastric plexus. This operation may be performed by anyone trained to do abdominal surgery. The risk involved is slight, the technic is not complicated and local anesthesia may be used for most if not all of the operation, if desired.

The portion of the sympathetic nervous system which is removed is that known as the presacral nerve or superior hypogastric plexus. This plexus can readily be found if one looks for a triangle the base of which corresponds to a line uniting the two common iliac arteries at the level of the sacral promontory, the sides being these arteries and the apex of the triangle being the point of bifurcation of the aorta. This triangle occupies the lower third of the fourth lumbar vertebra, the last intervertebral cartilaginous disk and the fifth lumbar vertebra. The base of the triangle is about 7 cm. in length and the distance from the base to the apex is almost 6 cm. A large part of the left side of the triangle is occupied by the left common iliac vein, which arises from the inferior vena cava and passes downward from beneath the right common iliac artery to accompany the left common iliac artery. The triangle is divided vertically into two equal halves by the middle sacral artery, which arises from the back part of the aorta just at its bifurcation and courses straight down to the upper part of the coccyx. Since this vessel is easily felt through the peritoneum it is often mistaken for the presacral nerve, which runs parallel to it. From the origin of the inferior mesenteric artery down to the bifurcation of the aorta, the sympathetic nerve fibers lie on the aorta, separated from it only by a layer of thin connective tissue. The branches of the plexus which accompany the left common iliac vein are separated from this vessel by areolar tissue, making elevation of the nerve easy. However, as the nerve fibers go still far-

ther down, they lie on the perichondrium of the last lumbar vertebra, and the cartilaginous disk between this vertebra and the sacrum. At this point the plexus lies above the middle sacral artery and veins.

The entire triangle is covered with peritoneum; hence the nerve plexus lies between the peritoneum and the underlying bones. The fibers are not adherent to the peritoneum, but are separated from it by more or less fatty tissue, depending on the obesity of the patient.

Two questions may properly be raised. One is whether the large fibers of the sympathetic system are really sensory. Ranson says that proof of this was offered more than twenty-five years ago by Edgeworth and that he confirmed Edgeworth's observations. If the roots of the spinal nerves are cut proximal to the spinal ganglions, all the motor fibers degenerate, but the sensory fibers remain.

The hypogastric plexus produces vasoconstriction of the blood vessels of the internal genital organs and it inhibits the secretion of the genital glands, whereas the parasympathetic nerves produce the opposite effect. Section of the superior hypogastric plexus does not alter the normal menstrual cycle nor does it interfere with uterine contractions during labor. Likewise, section does not produce glandular atrophy or any disturbances in the motor function of the bladder or rectum. Therefore, the nerve fibers of the superior hypogastric plexus are sensory and not motor. They carry the sensations from the internal genital organs to the medullary centers. Hence resection of the portion of the superior hypogastric plexus above the hypogastric ganglion is a simple way of relieving a patient of severe pain arising in the pelvic organs.

The second question that may be raised concerns the possible harm done by removing a portion of the sympathetic nervous system. Ranson states that Cannon and his students completely removed from cats "the sympathetic chain on both sides, from the highest cervical to the lowest sacral ganglion. Such completely sympathectomized cats have lived under laboratory conditions for many months. Everything indicates that

almost any part of the sympathetic system can be removed without seriously endangering life."

**Technic of Pelvic Sympathectomy.**—The technic of pelvic sympathectomy is as follows: The patient should be placed in the Trendelenburg position after a midline incision has been made from the umbilicus downward toward the pubis for about 10 to 12 cm. After the peritoneal cavity is opened, the small intestine is packed off and the sigmoid and rectum are pushed to the left side and held there with a wide retractor. The uterus, adnexa and bladder may then readily be inspected and palpated. One may detect a complication, that can be remedied by a surgical procedure. The region of the lower two lumbar vertebrae and the upper part of the sacrum is exposed to view. In thin women, it is possible in some cases to see the presacral nerve immediately beneath the peritoneum. Whether or not the nerve is seen, the parietal peritoneum above and in the middle of the sacral promontory is elevated and incised with scissors. This incision is extended upward for about 4 or 5 cm. and for a similar distance down along the sacrum. When the peritoneal flaps are pulled aside, a fibrocellular connective tissue layer will be exposed, covered by more or less adipose tissue. This tissue can easily be separated from the peritoneum and the lower end of the aorta without danger. It is in this layer that the presacral nerve lies. With an aneurysm needle the tissue is elevated at the bifurcation of the aorta and the dissection is carried to a still higher level. As this is done, it will be found that in most instances the tissue spreads out triangularly. The middle sacral artery should be pushed away from the nerve, but if it is injured it can readily be ligated.

After the dissection is carried as high as it is desirable to go, the layer of nerve tissue is separated from the underlying tissue down past the sacral promontory into the pelvic cavity. In this region the plexus has divided into two hypogastric nerves; hence it is necessary to dissect one of these nerves at a time. At least 2 or 3 cm. of each hypogastric nerve should be resected in addition to 4 or more centimeters

of the superior hypogastric and the intermesenteric plexuses. The fibrous tissue layer, which contains the hypogastric nerves, is much more resistant than that which contains the presacral nerve. As the dissection is carried out, nerve filaments projecting outward will be encountered. These should be followed as far laterally as possible before they are cut. In most instances, ganglions will be included in the resection. The dissected tissue should preferably be removed in one piece. It is not necessary or advisable to ligate the presacral nerve or the hypogastric nerves before cutting them, because the only blood vessels in intimate contact with them are insignificant vasa nervorum. Very rarely does one encounter bleeding that requires more than simple temporary pressure to check it. (When the mesosigmoid is very short, care must be exercised to avoid injury to the inferior mesenteric vessels.) After the nerve is dissected, the posterior parietal peritoneum is sutured with plain catgut and the abdominal wall is closed in the customary way.

Thus far my associate and I have performed 50 sympathectomies. We have found that if all women who have excruciating pain associated with carcinoma of the cervix are subjected to this operation only about 50 per cent will be relieved of their pain. However, if the patients are properly selected almost all will be freed of their pain.

The women who can definitely be relieved of their suffering by sympathectomy are those who have pain in the middle of the lower abdomen, pain low in the back, rectal tenesmus, bladder pain and pain associated with vesicovaginal fistulas. The women who cannot be helped much by sympathectomy are those who have pain in the sacrum due to fixation of the parametrium, pain referred from the region of the sacro-iliac joint into the thigh posteriorly and laterally, pain down the anterior surface of the thigh due to involvement of a gland in the obturator canal and pain due to hydronephrosis and hydro-ureter.

Pelvic sympathectomy is also curative of most cases of intractable dysmenorrhea where every form of therapy has

been tried and failed. Naturally this form of treatment for menstrual pain is heroic and hence it should be used only as a last resort.

**Chordotomy.**—The operation known as chordotomy should be attempted only by one skilled in neurologic surgery. The operation consists in the removal of a number of laminae, opening the dura mater and incising one or both anterolateral columns of the spinal cord as necessary. If the incision in the cord is not accurately placed, the pain may not be completely relieved because insufficient fibers were sectioned or the motor pathways (pyramidal tracts) may be damaged, resulting in paralysis of the legs and interference with sphincter control. I have had no personal experience with this operation.

**Pain Following Operation.**—There are occasional instances where distressing pain either arises or persists following an operation on the pelvic organs or in the lower abdomen. If a second operation is performed because of the pain it seldom gives relief because usually no cause for the pain can be found. In most of these patients, relief from the pain can be obtained by a pelvic sympathectomy.

**Conclusion.**—Any procedure which will relieve women of excruciating or constant pain is worthy of a trial. For the severe pain which is associated with malignancy of the female genitalia, drugs are unsatisfactory. There are three operations which can give most of these women relief. In the order of their simplicity they are the intraspinal (subarachnoid) injection of absolute alcohol, pelvic sympathectomy and chordotomy. The subarachnoid injection of alcohol should be tried first because it entails the least risk and gives relief in the vast majority of cases. Resection of the superior hypogastric plexus is more risky because it necessitates opening the abdominal cavity, but the risk is slight and the operation can be performed by anyone with surgical experience. Chordotomy on the other hand requires special technical knowledge.

In addition to the unfortunates who have advanced carcinoma there is a group of women who suffer inexorably during each monthly flow. For those who have not been helped by

medication, dilatation and curettement and other means, the operation of pelvic sympathectomy offers instant relief in the majority of cases. Likewise this operation will prove helpful in the cases where annoying pain follows an operation in the pelvis.

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## CLINIC OF DR. ISADORE PILOT

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#### SEPTIC SORE THROAT: CLINICAL AND BACTERIOLOGICAL CONSIDERATIONS

A SEVERE type of tonsillitis is usually designated as septic sore throat. Such marked reactions in the throat are particularly striking in infections due to the hemolytic streptococci. From the point of view of serious and fatal complications the significant septic sore throat has been observed in epidemic form, as milk-borne septic sore throat. Most sporadic cases appear as a mild sore throat or tonsillitis, but occasionally a similar intense type is encountered resembling in severity the epidemic form but not related to milk. The complications in such sporadic cases are often serious and deserve our special consideration.<sup>1</sup>

Acute throat infections present an extremely variable clinical picture. Several factors determine the local and general symptoms. These are, the virulence of the organisms, the dosage of these bacteria, the amount of lymphoid tissue in the oropharynx and most important the reactivity of the patient. Variations in these factors result in either mild or severe sore throat. A large dose of virulent streptococci in a patient with considerable lymphoid tissue and a lowered general resistance lead to a marked sore throat and general symptoms of sepsis that are characteristic of septic sore throat.

**Etiology.**—The bacteria most often involved in throat infections are the hemolytic streptococci. In our experience 50 per cent or more of the sore throat encountered in daily practice appear to be due to the streptococci. Apparently all human types of *S. hemolyticus* are responsible. The strep-



tococci yielding scarlet fever toxin cause sore throat with a characteristic rash of scarlatina in susceptible persons. In the Dick negative the streptococci may still be responsible for sore throat of a variable severity. Severe septic types are often associated with the scarlet rash and in their tendency to complications and sequelae septic sore throat and severe scarlet fever behave alike. The streptococci of erysipelas are also capable of producing sore throat. These strains are more difficult to identify. Erysipelas may originate from these streptococci invading the skin possibly through an abrasion about the nose or ear, particularly if there is a sinusitis or purulent otitis media that complicates the throat infection.

The most severe type is observed in acute throat infections due to the encapsulated mucoid hemolytic streptococci known as *Streptococcus epidemicus* (Davis). These peculiar properties identify these streptococci readily and have aided us greatly in investigating sporadic sore throat. In milk-borne epidemics these streptococci have always been the source of the mastitis in the cow whose udder sheds millions of these bacteria per cubic centimeter of milk. When raw milk containing *S. epidemicus* is consumed the dosage of infection is massive and a very severe type of sore throat infection results. Serious complications and an occasional death are associated with most milk-borne epidemics. In sporadic cases due to *S. epidemicus* the mode of infection is not through milk but through carriers or active cases. The dosage of the infecting bacteria is much smaller therefore, than in the epidemic type and the reaction of the throat milder. Occasionally the sore throat in the sporadic case may be severe and dangerous. Indeed when a very severe sore throat is observed, the encapsulated streptococci should be suspected. In a series of streptococcic sore throats of the sporadic type 10 per cent of the strains proved to be *S. epidemicus*. The complications and sequelae in this smaller group were more numerous and serious than in the other 90 per cent.<sup>2</sup>

A large number of the streptococci causing sore throat are not identified with *S. epidemicus*. *S. erysipelatus* or *S. scar-*

latinae. Little is known about their epidemiology and distribution. They may have considerable virulence and may cause sore throat and complications like that of the specific streptococci.

Among the organisms other than streptococci causing sore throat the pneumococci are most serious and often not recognized. These encapsulated diplococci are often very virulent and responsible for an infrequent but severe sore throat that may be very septic in its behavior. In two instances the pneumococci were recovered from the throat and the suppurative lesions of the neck in patients who were desperately ill. One succumbed and at autopsy the pneumococci were found in the pus associated with an extensive thrombophlebitis of the common facial vein with its tributaries, and in the embolic abscesses of the lungs. *Staphylococcus aureus* was isolated in pure form in four cases of sore throat.<sup>2</sup> Together with the nonhemolytic streptococci they are the cause of a mild form of sore throat. The diphtheria bacilli and Vincent's spirochetes are responsible for a characteristic variety of sore throat, but often the associated streptococci and pneumococci may modify the throat condition and render the condition more septic.

The essential changes in septic sore throat occur in the lymphoid ring of the pharynx. The faucial tonsils become enlarged, edematous and purulent exudation develops on the surface and in the crypts. If the faucial tonsils have been previously removed the lymphoid tissues of the pharynx and at the base the tongue become similarly involved. The spread of infection may be in one of several directions. The extension through the nasopharynx, the eustachian tube, middle ear, mastoid and meninges has been well recognized and emphasized. The pathogenesis of general sepsis has been less clearly understood. So-called "primary streptococcus peritonitis" has been ascribed to a primary hematogenous infection from the throat. Recent studies have pointed out the possibility of the streptococci passing through the depressed gastric juice unharmed to the intestine where they migrate

through the wall to the peritoneum. The spread to the neck and large veins has also been recently pointed out. Fatal cases of septic sore throat have been assumed to be the result of a septicemia from the throat, but careful study has shown that many develop sepsis from a thrombophlebitis that extends from the veins of the tonsils to the common facial and jugular vessels. The streptococcic pneumonia may therefore be embolic in origin, as well as the result of aspiration or lymphatic extension along the bronchi.

**Symptoms.**—It is needless to describe the symptoms of ordinary sore throat, but the striking features of the more severe and septic cases should be pointed out. At the onset the fever may be high and pulse very rapid. In one instance the temperature was 107° F. Upon examination early the only finding in the entire examination may be a redness of the lymphoid structures of the mouth. Swelling from edema and purulent exudation develop in twelve to twenty-four hours. White patches and intense redness are noted on the second and third days. The membrane in a streptococcus throat as a rule is readily wiped away although the orifices of the crypts may still appear as white spots after swabbing. The pneumococcus produces a more adherent membrane resembling in this respect diphtheria. Fever and tachycardia are sustained for three to five days and then drop slowly in two or three days. Within this period adenitis, otitis media, peritonsillar abscess, parapharyngeal abscess, cellulitis of the neck, or peritonitis may develop. Complications should be suspected if the patient is unable to open the jaws freely and tenderness and induration appear at the angle of the inferior maxilla. In some instances with suppurative processes in the loose tissue of the neck, the lower jaw may be so restricted in its motion as to render examination of the throat difficult. With complications, the fever and pulse rate remain high and the septic state more marked. A severe chill or chills may be indicative of thrombophlebitic involvement of the veins of the neck. In such instances pains in the chest, signs of

pulmonary involvement may appear quickly and lead to a fatal termination.

In patients without tonsils the clinical picture due to identical bacteria is modified. No doubt tonsillectomized persons have less sore throat, but instead many have "colds" and upper respiratory infections. In these individuals the streptococcus infection manifests itself usually with an abrupt onset, chilliness, fever  $102^{\circ}$  to  $105^{\circ}$  F. and rapid pulse. Prostration and muscular pains are marked as in influenza, but the pulse is rapid and not relatively slow in proportion to the temperature. Upon examination there may be no findings except for some redness of the pharynx. On the following day the lymphoid follicles may become swollen and covered with exudate. Soreness of throat as a symptom often is absent or only evident as a raw feeling at the base of the tongue. Cough and chest pains may develop, but the lungs and pleurae yield no signs of involvement. Pleuritis and pneumonia, in spite of these common symptoms, are unusual complications. Adenitis is less common than in patients with tonsils, but otitis media is not infrequent. In our experience cellulitis and thrombophlebitis of the fatal type are observed only in the tonsillar forms of septic sore throat. Persons with tonsillar tags develop sore throat with a clinical picture in relation to the amount of lymphoid tissue still present between the tonsillar pillars. Usually the tonsillar remnants become swollen, red, and covered with exudate.

**Complications.**—These most often develop during the first week of illness. Occasionally after a period of convalescence of a week or two a recurrent sore throat, fever and complications of adenitis, otitis, etc., may arise. At this stage, as the result of a possible state of hypersensitiveness to the streptococci, polyarthrititis, endocarditis resembling the rheumatic type may ensue. In a similar way, erythema nodosum and acute glomerulonephritis may appear as sequelae. In the patients with late complications and sequelae a careful examination of the flora of the throat will reveal the persistence of

the hemolytic streptococci in large numbers in swab cultures of the throat, but none in cultures made of the blood.<sup>1</sup>

**Diagnosis.** The diagnosis of septic sore throat is not difficult. Bacteriological examination to exclude diphtheria is very important. To demonstrate the causative bacteria, particularly the hemolytic streptococci, swab cultures should be made of the exudate of the throat, avoiding contamination from the saliva and sputum. The swab should be streaked on the surface of blood-agar plates and in addition inoculated into melted tubes of blood agar which are poured into petri dishes. The latter method will yield hemolytic streptococci that may be overgrown by other organisms on the streaked plates. The poured plates also yield a more accurate picture of the relative number of streptococci. To bring out the mucoid encapsulated streptococci (*S. epidemicus*) ascites fluid is added to the infusion blood agar in proportion of 1 part of ascites fluid to 5 of agar. In severe cases with complications the *S. epidemicus* is a frequent offender because of the more invasive character of the encapsulated organisms. If sore throat appears in epidemic form, the epidemicus should be suspected and if found milk should be suspected as the source of the epidemic infection. No epidemics have been reported as yet from pasteurized or certified milk. Extensive epidemics continue to be traced to raw milk derived from cattle with mastitis due to *S. epidemicus*.

The diagnosis of streptococcus sore throat may be difficult in connection with tonsillectomized persons. Undoubtedly many person with respiratory infections are designated as influenza which in reality are due to the *Streptococcus hemolyticus*. If clinical features are inadequate for differentiation, a swab culture of the throat for hemolytic streptococci may aid in deciding the true clinical state.

In severe cases with apparent complications the recognition of peritonsillar abscess, thrombophlebitis of the vessels are exceedingly important. A chill, high fever, leukocytosis, inability to open jaws, pain and tenderness in the tissues about the angle of the jaw, all point to serious involvement. The

diagnosis of thrombophlebitis is not easy, but if definite should be made quickly and decisively so that surgical ligations and drainage may be immediately instituted.

**Prophylaxis and Treatment.**—In the epidemic form the source of septic sore throat is raw milk from a cow with mastitis due to a hemolytic streptococcus identified as *S. epidemicus*. To prevent further spread milk should be boiled until the responsible cow is located and excluded. In the sporadic form, sore throat is spread by contact with patients or carriers of dangerous streptococci. It is necessary, therefore, to isolate acutely affected patients exactly as in scarlet fever. If the patient is placed in the hospital because of the complications, these precautions should be insisted upon in order to protect other patients.

In active management of a patient the same measures are carried out as in ordinary tonsillitis. The patient should be watched closely for the development of complications. No specific antistreptococcus or antitoxic serums are available for all cases and in their absence one would be justified to employ a polyvalent streptococcus serum or even the scarlet fever antitoxin in the more serious cases, particularly when complications develop. In some instances it has been possible to employ convalescent serum or blood transfusion from persons who have recently recovered from sore throat. Our experience with convalescent scarlet fever serum in severe complications from septic sore throat is limited.

The treatment of the suppurative complications of the neck and the thrombophlebitis of the facial veins require the services of a surgeon who has thorough knowledge of the anatomical relationships of the structures of the neck to the lymphoid tissues of the throat. Ligation of the facial and jugular veins in severe septic types with chills may be a life-saving procedure.

Convalescence in sore throat is often neglected and may result in the appearance of complications and sequelae in the third and fourth weeks after the onset. If the throat remains deep red, the tonsils large and edematous, there is good indi-

When a tonsillar infection spreads beyond its original confines, that is, when a tonsillitis becomes a peritonsillar abscess, the new inflammation is confined to the connective tissue above described, between the tonsil and the superior constrictor muscle.

Should one of these extratonsillar inflammations spread and in one way or another pass through the superior constrictor muscle, the process is now in the deep tissues of the neck in an area called the parapharyngeal or pharyngomaxillary space or fossa. It is the invasion of this territory which is characterized by signs of sepsis in addition to other symptoms and which is so dangerous to the life of the patient.

The anatomy of the parapharyngeal space or fossa has been concisely and admirably described by Mosher. "The inner boundary of the fossa is the superior constrictor with the tonsil attached to it. The outer boundary *below* is the internal pterygoid muscle lining the inner surface of the ascending ramus of the jaw and mating the masseter on the outside. The outer boundary *above* is the parotid gland, the gland at this point not being covered with fasciae. Posteriorly, the prevertebral muscles and the prevertebral fascia bounds the fossa. The fossa is divided into unequal parts by the styloid process and the muscles rising from it. These are in front of the great vessels and protect them. On the posterior wall near the middle line on the front face of the second cervical vertebrae, there are two lymphatic glands which drain the nose and the upper pharynx and are in chain with the deep cervical glands."

The anterior or muscular or prestyloid compartment contains no large vessels or nerve trunks. It communicates with the parotid space through a defect in the fascia of the latter and is in close relationship to the submaxillary fossa.

The posterior, vascular or retrostyloid compartment contains the carotid arteries, the jugular vein, the glossopharyngeal, vagus, hypoglossal, spinal accessory and the cervical sympathetic nerves.

It is clear that pus in the posterior or vascular compart-

ment, hence, has a clear pathway from the skull and its contents above, to the mediastinum below.

There are at least three ways by which a tonsillar or peritonsillar infection may invade the parapharyngeal space. The first is by means of a retrograde thrombophlebitis of the tonsillar veins to the internal jugular vein. The second is by

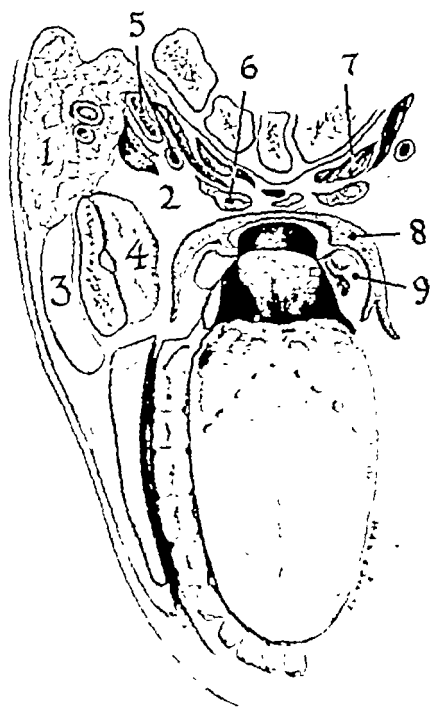


FIG. 127.—Cross section of the neck at through the second cervical vertebra showing the pharyngomaxillary or parapharyngeal space. (After Mosher.) 1, Parotid gland; 2, parapharyngeal space; 3, masseter muscle; 4, internal pterygoid muscle; 5, great vessels; 6, lymph nodes; 7, prevertebral muscles; 8, superior constrictor muscle; 9, tonsil.

way of a lymphangitis and lymphadenitis producing, because of the close attachment of the deep cervical glands to the internal jugular vein, first of all a phlebitis and then a thrombosis of the vein. The phlegmonous changes following a lymphangitis may also attack the veins secondarily. Finally, by direct extension, through the superior constrictor muscle, pus



from a peritonsillar abscess or pus produced by breaking down of inflamed glands, may involve the fossa and bathe its contents, attacking with ease the jugular vein because of its thin walls. Combinations of all these three types probably exist in most instances.

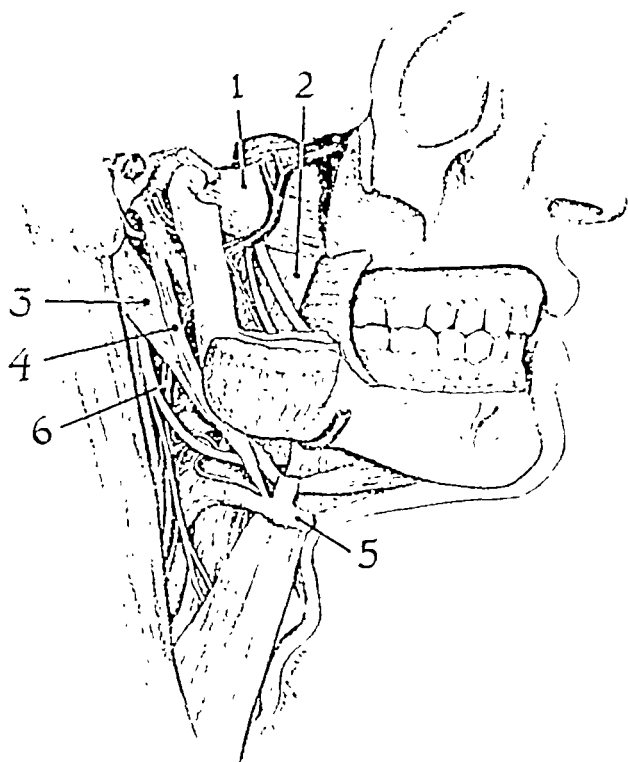


Fig. 128.—Dissection of lateral aspect of neck and pterygoid region. (After Bock.) 1, External pterygoid muscle; 2, internal pterygoid muscle; 3, digastric muscle; 4, stylohyoid muscle; 5, hyoid bone; 6, external carotid artery.

The symptomatology of parapharyngeal space infections may be best handled, perhaps, by describing a typical case. Following an attack of tonsillitis, a patient develops a peritonsillar abscess. The usual treatment directed toward this condition fails to give speedy relief. Inability to open the mouth widely or trismus appears. Now trismus is a common

symptom of peritonsillar abscess, but it disappears quickly after drainage has been instituted. Its persistence, in spite of adequate drainage, or its reappearance after having previously disappeared frequently means that the infection has spread beyond the usual area involved in the ordinary quinsy. Its presence in parapharyngeal space infections is due to an inflammatory infiltration involving the internal pterygoid muscle which forms one of the walls of the space.

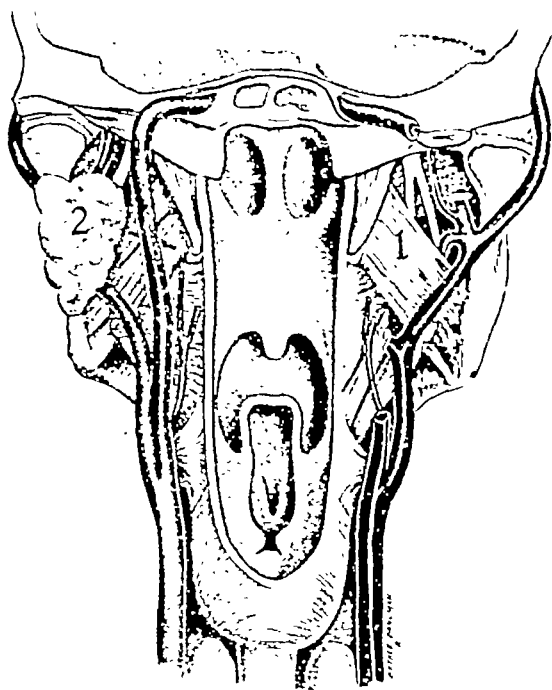


Fig. 129.—The parapharyngeal space from behind. The pharynx has been opened. (After Bock.) 1, Internal pterygoid muscle one of the boundaries of the space; 2, parotid gland, showing its close relationship to the space.

Fever soon appears. It is usually septic in type, but may be high and continuous. Chills are usually present and come with increasing frequency. A chill at the onset of a tonsillitis or peritonsillar abscess is not uncommon. Repeated recurrence of chills, however, is an ominous sign, and should cause the physician to extend every effort to arrive at a satis-

factory explanation. He must be sure to rule out leukemia, agranulocytosis, pneumonia and all other conditions which could produce this state of affairs.

Most of the time in addition to above symptoms, a brawny induration develops in the neck about the angle of the jaw. Rapidly progressing types and those in which the chief pathology is a retrograde thrombophlebitis from the tonsillar veins to the internal jugular vein may show little or no external swelling in the neck. They may, however, show some tenderness along the course of the vein. The more slowly progressive and benign forms, as a rule, are accompanied by the above described induration. Careful inspection of the pharynx, furthermore, may show some bulging of the lateral pharyngeal wall on the affected side, and the homolateral soft palate may be sluggish in its movements. In addition, there will be considerable pain and difficulty on swallowing.

Having established to his satisfaction that the deep tissues of the neck have been invaded, what is the surgeon to do? The treatment resolves itself chiefly into two parts. Pus is to be evacuated and a thrombosed jugular vein must be ligated or rather resected. In most uncomplicated instances, adequate drainage is sufficient to cause a disappearance of the symptoms. If, following drainage, there is not the expected relief, the internal jugular vein must be inspected and properly handled.

In those cases wherein the pathology is primarily a thrombosis of the internal jugular and there is no evidence of pus in the parapharyngeal space, one proceeds at once to the resection of the vein.

Some authorities insist that in addition to the above the tonsil on the diseased side should also be removed. In the event both tonsils are involved, it becomes more difficult in the absence of external signs to determine which internal jugular vein is involved. It is recommended under these circumstances first to explore the side on which the tonsil appears to be most involved.

Pus may be reached and evacuated in a number of ways.

The abscess may be evacuated by way of the pharynx. After preliminary tonsillectomy a long curved hemostat is thrust at the point of greatest bulging through the superior constrictor muscle into the parapharyngeal space. Such a procedure, according to Hall, will in all probability reach only the anterior compartment of the space. A general anesthetic should not be used, for the danger of asphyxia is great. Infiltration anesthesia is risky because additional infection may be carried through the infected field into the deep tissues. It is better

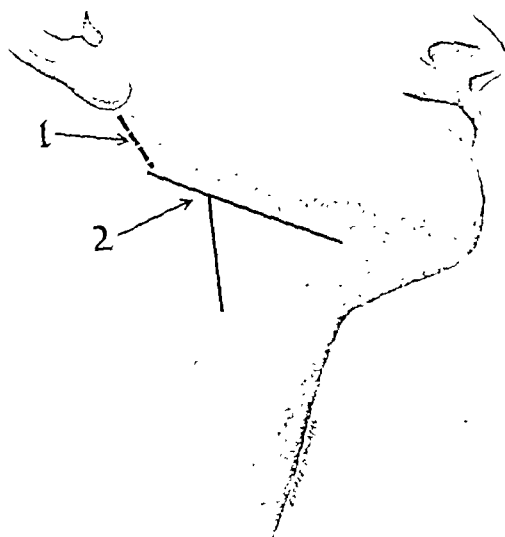


Fig. 130.—1, Incision for "simple" incision. In the illustration the dotted line is somewhat long and too high; 2, incision as advocated by Mosher.

to apply cocaine locally, and in addition to obtain some blunting of sensation by anesthetizing the sphenopalatine ganglion as recommended by Guttman for the opening of peritonsillar abscesses. It is obvious that the pharyngeal approach is of limited value and is not applicable in the absence of a pharyngeal swelling; it needs to be preceded often by a preliminary tonsillectomy; frequently in the presence of a peritonsillar abscess.

The external approaches are usually favored by men of

experience. They should be used most of the time and when there is no pharyngeal lead or when the results of opening by way of the pharynx are not satisfactory after a wait of twenty-four to forty-eight hours. The "simple" external approach may be used at times with satisfaction. The angle of the mandible is found two fingerbreadths below the lobule of the ear and on a line with the mastoid tip. A vertical incision is made just behind the angle through the skin and subcutaneous tissues. A curved hemostat or scissors carried in an upward and inward direction through the deep fascia on to the internal aspect of mandible, *i. e.*, along the internal pterygoid muscle (Batson), enters the parapharyngeal space. Neither of the two above approaches permits inspection or treatment directed toward the internal jugular vein.

On the continent, especially in the Germanic countries, the approach popularized by Marschik is used almost exclusively. The skin incision is along the anterior border of the sternomastoid muscle, with its middle at the level of the angle of the mandible. The deep cervical fascia is exposed, and at the level of the angle of the jaw is incised or opened by blunt dissection in the direction of the skin incision. Further orientation depends on finding the stylohyoid muscle and the tendon of the digastric muscles. These are beneath the angle and run from above and behind downward and forward. At this point the tendon of the digastric perforates the fibers of the stylohyoid. Both muscles are retracted downward. Upward and forward blunt dissection exposes the anterior parapharyngeal space. Blunt dissection with a forceps or finger beneath the digastric carries one to the posterior parapharyngeal space and the carotid sheath. Following the stylohyoid the finger palpates the styloid process and may be carried upward to the base of the skull.

In this country, Mosher's advocacy of the submaxillary fossa approach to pus deep in the neck has made a deep impression. He recommends a generous T-shaped incision. The skin flaps are retracted and the lower border of the submaxillary gland defined. The gland lies between the two bellies of

the digastric muscle as in a sling, and is lifted upward. The facial vein is tied and cut. The finger or blunt forceps carried upward beneath the posterior belly of the digastric muscle finds the carotid sheath and pus if it is present. The styloid process is easily palpable and pus accumulations about the base of the skull may be reached. This exposure, better than the preceding one, allows for examination of the base of the tongue, and the floor of the mouth as well as the entire neck

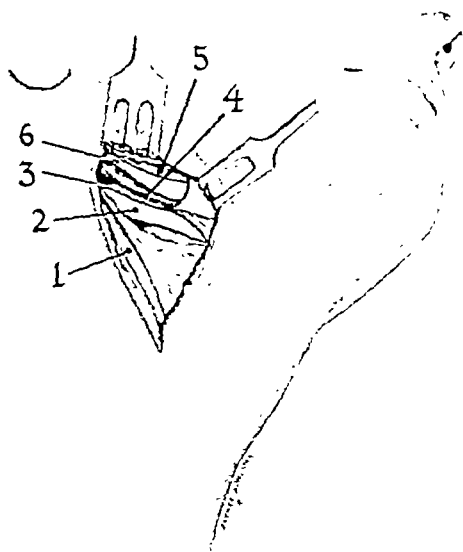


Fig. 131.—Operative approach according to Marschik. (After Wessely.)  
1, Sternomastoid muscle; 2, digastric muscle; 3, stylohyoid muscle; 4, styloglossus muscle; 5, stylopharyngeus muscle; 6, loose fascia of the pharynx.

from the base of the skull downward. The internal jugular vein is easily inspected and ligation and resection carried out. (See Fig. 130.)

Finally, the parapharyngeal space may be exposed after Kramm's recommendation by a retromandibular approach. This has the claimed advantage of exposing the parapharyngeal space from the base of the skull to the angle of the mandible, and is said to be quite easy to do. The incision is car-

ried through the skin at the anterior border of the sternomastoid muscle from the tip of the mastoid to 2 cm. below the angle of the jaw. Great care is necessary at this point to define the lower pole of the parotid gland, which is freed by blunt dissection and carried forward. Beneath and medial from the sternomastoid muscle the posterior belly of the digastric muscle now appears.

Somewhat deeper and more medial the internal jugular vein appears. One or 2 cm. in front of and somewhat medial

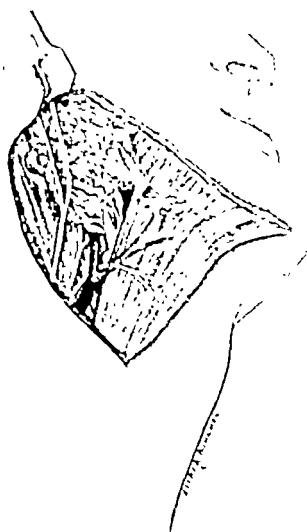


Fig. 132.—Dissection of parotid region. (After Tandler.) In the exposure as advocated by Kramm, the lower and posterior border of the parotid gland is dissected free and pulled upward and forward.

to the vein the styloid process is opened by blunt dissection and the process cleared from its tip upward as high as possible.

A small or medium-sized nasal speculum is passed into the prepared cavity with blades closed. When the speculum is opened the styloid muscles separate, the styloglossus anteriorly, the stylohyoid posteriorly, and the whole anterior parapharyngeal space is exposed. Further use of the speculum exposes the vascular sheath back of the styloid process.

The advantage of this exposure is that it brings one to the

center of the infected area. The greatest difficulty is encountered at first in freeing the lower pole of the parotid gland. Thereafter the dissection proceeds with ease. The styloid process, a most important landmark in these exposures, is easily exposed and no large vessels are in the way excepting the internal jugular vein which one is anxious to see and handle surgically, if necessary.

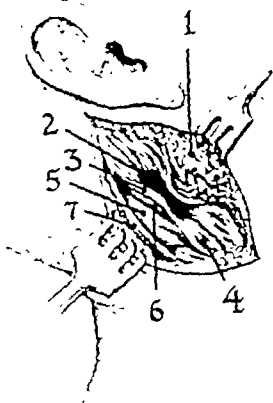


Fig. 133.—Exposure of parapharyngeal space as advocated by Kramm 1, Parotid gland; 2, parapharyngeal space; 3, styloid process; 4, stylohyoid muscle; 5, digastric muscle; 6, internal jugular vein; 7, sternomastoid muscle.

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JAUNDICE: A BRIEF DISCUSSION OF DIAGNOSIS FOLLOWED BY A PROPOSED MEDICAL MANAGEMENT

THE principal decision which a physician should hasten to make when he sees a patient with jaundice is whether to advise surgery or try medical management. It is just as important in this year of progress and laboratory enlightenment to elicit a most detailed and careful history as it ever was before. The interpretation of the many tests to measure liver function still depends on the clinical conditions as shown by the history, the physical examination, roentgen studies, and the usual laboratory procedures. If surgical measures are finally chosen, it is usually our experience that patients seem instinctively to refuse or defer an operation in painless jaundice. This patient deferred several times. Medical management must be advised not only to help the condition if it can be helped, but to uncover latent symptoms so that the conditions difficult to diagnose, primary carcinoma of the bile tract, carcinoma of the head of the pancreas, and silent stone, will not be allowed to develop past the point of helpful surgery.

The patient I am showing you today illustrates the necessity of briefly reviewing the increasing physiologic knowledge of the liver and bile tracts so that we may benefit by better clinical judgment. Today we can bring out only an occasional point so completely discussed by Ivy<sup>1</sup> in his recent review with a bibliography of 553 articles covered. Each year, through advances in the fact-finding sciences of physiology and pathology, we are able either to *discard* or justify our remaining clinical concepts.

The decision as to policy of treatment which we faced in this patient is a common dilemma. Even with our better understanding of liver processes it is still difficult to be correct in the choice of either medical or surgical treatment of jaundice. To illustrate these points in differential diagnosis I will tell the story of C. S.

This strongly built, well-nourished man, fifty years of age, came to our clinic in February, 1933. He was deeply jaundiced, had no pain, not very sick, and complained only of some fatigue, belching and constipation. He remembered having a painful jaundice five years before which cleared up in a few weeks without surgical aid. As he recalled his sensations in the previous attack, he did not seem much impressed by the pain but always pointed to the right costal margin. He did not recall radiation to the shoulder blade. It was definite that the first attack under our observation was at least less painful as he senses only an epigastric fullness. He stated that he lost 40 pounds during seven weeks. In December, 1932 he lost his appetite. Following this, the jaundice began with a slow insidious onset. He was never seriously ill nor had he ever noted any gastro-intestinal symptoms except for his 1928 jaundice. He had been in perfect health from 1928 to December, 1932. There was nothing in his habits or occupation to suggest contact with carbon tetrachloride, chloroform, tribromethanol, phenylhydrazine, phosphorus, or trinitrotoluene. He was a machinist, never drank alcoholic beverages; not even coffee. He went to bed early, had a happy home life with good cooking and never worried. As he never took any kind of medicine we could rule out the other toxic jaundices due to the cinchophens and arsphenamines. He had eaten few carrots and no mushrooms. Some of the above conditions have been discussed by C. A. Elliott<sup>1</sup> and Walter Nadler,<sup>2</sup> Starr,<sup>3</sup> Bloch and Rosenberg<sup>4</sup> and Carroll,<sup>5</sup> which form a good background for clinical understanding of the liver and bile tracts.

Physical examination showed no fever or enlargement of the spleen. There was no history of intermittent fever with chills as with a "ball valve" stone in the common duct. He did not have the greenish-yellow color as in Gaucher's disease and the normal spleen definitely ruled that out. A negative Wassermann test turned our minds from a luetic cause of jaundice. A coincident Banti's disease was ruled out by the absence of spleen enlargement and hypochromic anemia. There were no other signs of decompensation to go with the jaundice associated with a failing heart. There were no enlarged collateral veins visible beneath the skin of the abdomen and not enough enlargement of the liver to suggest cirrhosis. The liver edge was smooth, enlarged three fingers and very faintly tender. There were no hard nodules and not enough enlargement of the liver to suggest the jaundice from a liver so full of metastases as to bring on jaundice. This condition is usually quite terminal and easy to diagnose by a careful search. The gallbladder could be palpated and was not tender. With no fever it is hard to conceive of yellow fever. I have seen a patient with undulant fever who had coincident mild jaundice but again we can rule this out.

The usual blood studies ruled out the jaundice with pernicious anemia, sickle cell anemia and very probably hemolytic jaundice. The patient had never noted blood in the urine and our tests showed none so that paroxysmal hemoglobinuria could be ruled out. Malaria was not found and there were no symptoms or history suggestive of "blackwater fever." The liver did not seem large enough to consider this a typical example of Hanot's cirrhosis. Apparently obstructive back pressure must either be quite marked or of a long duration or occur in a vulnerable liver to produce this old clinical picture. In Weil's disease there is usually fever, albuminuria and more malaise and aches than this patient had. After considering this array of clinical disorders together with a few not mentioned, such as Laennec's cirrhosis and Hodgkin's disease, I think you will agree in a movement toward pure pathology and physiology to simplify such a subject as this.

There are several diseases not yet ruled out even with the complete gastrointestinal roentgen study. These are aneurysms of the hepatic artery, dormant echinococcus cyst and peritoneal adhesions. Primary tumors of the gallbladder or bile tracts or the pancreas are consistently missed by the best roentgenologists. Gallbladder visualizations are risky procedures in jaundice. One was done on this patient largely for academic purposes after the jaundice had subsided somewhat. No stones were seen, the gallbladder partially filled and was very slow in emptying.

Surgery was advised because of a provisional diagnosis of possible carcinoma, although the history would indicate a silent stone with partial obstruction and secondary hepatitis. The patient decided to assume the risk of deferring the operation, which gave us the opportunity of using the usual liver function tests. Time does not allow the interpretation of each one during the course of observation from February, 1933 to May, 1935. During each of the three attacks which occurred, the urine was dark, the stools light. The gastric contents were examined frequently for the two-year period and showed a free acid of 40 to 60 at first, gradually falling to 30 to 40, since August, 1933. During the first three weeks after each attack the benzidine test was positive in the stomach contents and stools and at other times was negative.

Recently there has been an increasing interest in liver function tests accompanied by a widespread increase in their uses. These tests are certainly an effort in the right direction. Many times they are ordered by a busy physician as part of his ritual, in much the same way as useless metabolic rates. They may be blamed afterward for a bad decision which should have been based on more simple and obvious observations. As it turned out later in this instance they, together with the time elements, helped guide us to a better pre-operative diagnosis than the provisional one of carcinoma. Some of them require a highly trained laboratory staff and some are so complex as to lead to error. The interpretation

is extremely confusing in a mixture of pathological conditions, such as slight obstruction with moderate hepatitis.

The icterus index is quite simple and measures the yellow color of blood serum in units as compared to a 1:10,000 potassium bichromate solution. It is more satisfactory than skin color which changes shade slowly. It will show an increase in jaundice when urine does not always reflect the change. The abnormal readings begin at about 15 and are said to go over 300. It is difficult for us to make what we consider accurate readings over 200. This patient's maximums were 130, 80 and 160 in the three attacks. If it changes rapidly, we may allow ourselves to think of a changing obstructive process.

The van den Bergh reaction was taken up in this country soon after the World War. The apex of exact interpretation in the effort to differentiate medical from surgical jaundice was reached about 1929 to 1932. We have come more and more to use the results of this test cautiously. In obstruction the rise from a normal reading of 1 to 3 mg. rapidly rises to 15 to 30. In silent stone this does not differentiate from obstruction by neoplasm. In obstruction the immediate direct van den Bergh was supposed to be positive; the indirect positive. A delayed direct reaction was interpreted as reflecting a hemolytic form of jaundice. Where both obstructive and nonobstructive forces were supposed to be taking place simultaneously, as in toxic and infective jaundice, the biphasic reaction should occur. Jaffé's conception of so-called catarrhal jaundice being primarily a hepatitis which we believe is correct, makes such interpretations most complicated and unsound. I believe until we know more, the practitioner should use more simple criteria. In most instances the intrahepatic damage has already begun to give the delayed direct reaction by the time the doctor is able to see the patient and make the test. Our patient showed 16, 5 and 18 in the three attacks. When considered together with the icterus index, we would think perhaps that the first attack was approximately 60 per cent obstruction and 40 per cent hepatitis, the second

largely hepatitis, and the last mostly obstruction with some hepatitis. As it happened this man was about correct, but such interpretations might just as well have led us astray unless we carefully questioned and examined the patient. N. C. Gilbert has tried injecting bilirubin 1 mg. per kilo into patients to study the degree of liver embarrassment. Bilirubin is very expensive and we consider this only as a "research step" in liver studies. We did not make this study in this particular case, although it should have been done.

The bromsulphalein test as described by Serby and Bloch<sup>6</sup> may be of use in the diagnosis of carcinoma of the head of the pancreas.

The blood cholesterol determinations are of some interest to those of you having technicians who make no errors. This is especially true when cholesterol esters are studied. When the liver is embarrassed the cholesterol usually removed by the liver is found increased in the blood stream. In obstruction the cholesterol goes up rapidly from the normal level of 180-200 to as much as 500 mg. If at the same time the cholesterol esters decrease disproportionately, *i. e.*, more than their 40 per cent drop to 20 per cent or less, it makes us suspect that intrahepatic damage is increasing in proportion to the obstructive process. This is clearly described by Ottenberg.<sup>7</sup>

The galactose tolerance test depends on measuring the loss of efficiency of the liver as a factor in carbohydrate metabolism. After 40 Gm. of galactose is given under basal metabolic conditions about 3 Gm. or less comes out in the urine in five hours. If more is excreted, we may conclude that at least something is deficient in carbohydrate metabolism; perhaps the liver. This would not help us in choosing either medical or surgical management of jaundice, but it has a distinct place in metabolism clinics to further knowledge.

This patient was jaundiced for seventeen weeks in his first attack in the winter and spring of 1933. This persisted in spite of the medical management to be described later. He cleared up, felt well from June, 1933 to July, 1934. He was very conscientious in his clinic visits for gastric and stool

analyses during the entire interim. He followed his diet most of the time. In July, 1934 the weather was very hot and jaundice recurred (the second attack referred to in discussion of liver function tests). This attack lasted only three weeks and was probably just a simple hepatitis with little obstruction as hinted by the icterus index and van den Bergh. All went well with him until he contracted an influenzal attack in January, 1935. He continued his work and felt very bad for a month, at which time he slowly redeveloped his jaundice. In February, 1935 he had more epigastric heaviness, but no actual pain. Thus the history of influenza suggested that hepatitis was the strongest factor, but the liver function tests pointed more to obstruction.

The many tests he had undergone were again explained to him and a third invitation for surgery was presented him. A note in the record at this time reads: "If there is a neoplasm it is not a fast growing one." The diagnosis became partial obstruction of the common duct with recurring hepatitis. The patient consented and operation in March, 1935 disclosed a small stone partially obstructing the ampulla of Vater with probable mild hepatitis. The surgeon thought it inadvisable to remove a section of liver for study. There were a few very small stones in a large thickened gallbladder. The stomach and duodenum seemed normal to Dr. H. E. Jones, who performed the operation. Cholecystectomy was performed and the patient made a good recovery and has felt well since.

We may conclude from this that a hepatitis or so-called catarrhal jaundice was secondary to a partial obstruction. The liver vulnerability was probably caused by a residual infection following the first obstruction in 1928; or the partial obstruction off and on since. Difficulties arose when the patient became fatigued; during hot weather, after cold infection, or after dietary indiscretions.

At the time this patient came to the clinic in 1933 we were on our ninth year in trying a new type of management for embarrassed livers and low-grade gallbladder inflammations

with or without stones. It may be briefly described in three stages and should be used only when medical management seems advisable after careful study.

In the presence of jaundice we follow conventional lines of absolute rest, plenty of fluids, excess carbohydrates, intravenous glucose, and rarely intravenous calcium gluconate. We are sparing in the protein allowance and begin a bland creamy diet described later as the jaundice subsides. Decholin or Epsom salts are not given in an active jaundice.

When the jaundice has subsided the first stage of management for all low-grade gallbladder disorders and liver dyscrasias is gradually begun. This is virtually a strict hourly feeding ulcer management including the usual cream, eggs, cereals, custards, gelatins and butter with three pureed cooked vegetables and two pureed cooked dried fruits. If there is pain, refer to surgery. The calories are gradually increased according to the patient's tolerance to about 3000 daily. Most authorities do not believe that the bile tract empties, such as cream, butter and eggs, should be used. This clinical management follows Ivy's and Jones' idea that overcoming stasis without quite overloading the embarrassed liver's ability may help rehabilitation toward its natural physiologic function. From our studies we believe the stomach outlet is usually in difficulty at such a time and should be protected by the small, frequent, neutralizing feedings. Remember the positive ben-zidine tests in the gastric contents for the first few weeks of each attack in this patient. Antispasmodics, such as tincture of belladonna, with phenobarbital are used routinely.

The second stage of management is withheld until the patient has nearly recovered and occult blood has been absent from the stools and stomach for some time. This is the addition of trial teaspoonful doses of Epsom salt or  $\frac{1}{2}$  teaspoonful doses of magnesium oxide replacing feedings at the estimated emptying time of the stomach. The patient should never be purged, and the amount should be cut down if more than one or two bowel movements per day result. If no pain, continue the first stage of medical management. If pain results, refer



the patient to surgery. This stage is as much diagnostic as therapeutic and answers the requirements for a management which will bring out latent symptoms.

The third stage is used only after the jaundice has gone and the patient reverts to the chronic bile tract and liver dyscrasia classification. This is the addition of decholin to the first stage treatment. According to K. K. Jones, this markedly increases bile flow in dogs. If there is pain, refer to surgery; if not, either continue on stage one or stage three.

Some of the most interesting findings in this management have been the gratifying results on the gallbladder dyscrasias of which there are a surprising number. These usually occur without jaundice. Psychic management with antispasmodics stronger than usual are of great assistance to the patients.

*The interrelation of diseases of the liver and bile tracts to duodenal disorder cannot be overemphasized.* We should seek always to protect stomach and duodenal lining in any treatment for jaundice or associated disorders. We should give every possible aid to smooth natural bowel peristalsis by avoiding any cathartics (except for diagnosis). The pureed cooked vegetable and dried fruits plus mucilose or metamucil can do a great deal in avoiding spasm of the bile tracts. This avoids back pressure and stasis which probably helps in the rehabilitation of inflamed liver cells and bile passages.

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### THE TREATMENT OF BRONCHIECTASIS

DILATATION of the bronchi was first called to the attention of Laennec by his pupil Cayol. In 1819, in the first edition of "*Traité sur l'auscultation médiate*" Laennec spoke of it as an extremely rare disease. By 1826 he had become impressed with its frequency. From that time until the present, as attention has been drawn to it and diagnostic methods have been developed, there has been a progressive recognition of its true incidence. Today it is known to stand second only to tuberculosis as a cause of chronic cough. In some hospitals it has been found in 7 per cent of all autopsies. It is probable that in this present gathering of 50 people there are 3 or 4 affected with it and I am certain that one rarely lectures on the disease to a class of medical students without having one or more come up afterward and say that they have the symptoms described.

Bronchiectasis varies greatly in the severity of the symptoms which it produces. Fortunately many cases are mild and those so afflicted lead long and active lives scarcely incommoded by their slight morning cough and expectoration. In its severer form, and the severity of the symptoms seems to bear little relation to the size of the dilatations, it is a terrible and distressing affliction, the frequent coughing spells, the foul breath and the necessity of expectorating great quantities of fetid sputum rendering the subject a social outcast. While fever, emaciation and systemic symptoms are extremely rare and most patients, even those with profuse expectorations,

appear to be in good health, the disease does threaten and shorten life. In a series of 200 cases which I studied, 50 per cent began before the tenth year, but of those over forty years old few or none dated the onset to childhood. This suggests that most of those affected in childhood succumbed to pneumonia, lung abscess, brain abscess or some of the other complications of the disease before reaching forty.

Bronchiectasis is one of the most difficult diseases to treat. Success is usually partial and often slight. The dilatations are permanent deformities which can be cured only by excision of the lung, and the chronic bronchitis is usually extremely resistant. While any one of a variety of remedies may give startling results in an occasional instance, too often all remedies fail. Today I wish to speak particularly of the treatment.

Sydenham wrote: "I have come to this conviction—that those who have directed their eyes and their minds the most accurately and diligently to the phenomena of disease will excel in eliciting and applying the true indications of cure." Having in mind this practical attitude toward clinical observations, I wish today, while speaking of bronchiectasis, to concern myself not with the dilated bronchi or their forms or causes, but with the chronic bronchitis to which they predispose. Dilated bronchi neither produce symptoms, impair health nor threaten life. They do favor the establishment of chronic infection and it is this that is the true disease. Since it is the bronchitis which must be treated, a consideration of its pathogenesis—the factors which favor its inception and determine its chronicity—should point the way to logical and successful treatment.

In all of the body cavities and tracts there are four conditions which incite infection and maintain it in a chronic state. These are:

1. Interference with the normal evacuation of secretions.
2. Persistent reinfection.
3. The presence of a foreign body.
4. Infection with tubercle bacilli or other resistant organisms.

In bronchiectasis the normal mechanisms for evacuation of secretions, the ciliary action of the epithelium and the peristaltic contractions of the bronchial musculature, are destroyed. These being out of function, gravity favors the accumulation and stagnation of secretions and the development of chronic infection. The rôle of gravity is of the greatest importance. Bronchiectasis is rare in any part of the lungs save the posterior and most dependent portions of the lower lobes. When it does occur in the upper lobes the etiology is either parenchymal fibrosis or bronchial obstruction and upper lobe dilatations are rarely complicated by chronic bronchitis or profuse secretion. These facts justify one in surmising that bronchiectasis, usually in its etiology, and practically always in its clinical manifestations, is a disease of posture—one of the many untoward results of man's assumption of the unnatural erect and supine positions. Whether or not gravity so hinders evacuation as to produce the dilatations or the diseases which produce them, it is certain that once the bronchi are dilated and the ciliary and peristaltic mechanisms compromised, gravity is the chief cause of the accumulation of secretions and the persistence of infection.

Persistent reinfection sometimes causes bronchiectasis and practically always plays a part in maintaining the infection. Chronic sinusitis is recognized as a cause of the disease and in nearly every case of bronchiectasis the sinuses are involved. In some instances they are the etiological factor and in others are secondarily infected from the continual spraying of the upper respiratory passages with the raised secretions. In all cases the chronic postnasal discharge adds constantly to the infection in the dilated tubes.

Foreign bodies, either of extraneous origin or broncholiths formed in situ, are not uncommon in bronchiectasis. When present, they are an important cause of profuse bronchial secretion.

Tubercle bacilli and other resistant organisms are probably not a factor in the chronic bronchitis of bronchiectasis. While the condition often complicates tuberculosis, chronic

bronchial infection with mixed organisms or parenchymal fibrosis probably produce it. It has been suggested that infection of the bronchial walls by fusiform bacilli and spirochetes causes the dilatations. Whatever may be the truth of this, once the dilatations are established, stagnant secretions in which develop any and all varieties of organisms cause the bronchitis and expectoration.

From these considerations of pathogenesis the following measures should be of value in clearing up the bronchitis of bronchiectasis:

1. The prevention of stagnation of secretions by postural drainage, induced cough, bronchoscopic aspirations and bronchial lavage.
2. The prevention of reinfection by cleaning up infection in the upper respiratory tract.
3. Search for and removal of foreign bodies or dilatation of bronchial stenoses.
4. Medication, either local or internal.

Concerning this last, I have had most success with extremely large doses of potassium iodide. In an occasional case the results have been striking. Stokes and the older clinicians favored tartar emetic. Repeated instillations of iodized oil have been strongly recommended by Ochsner and others. Good results are rare and it is probable that they are due to the systemic rather than the local action of the drug.

Many patients are better during the summer months, some entirely free from symptoms. Such cases are apt, but not certain, to be benefited by residence in a dry, warm climate. It is my belief that relief comes less from the quality of the air than from the avoidance of acute upper respiratory infections which are less common in equable climates. One patient of mine was practically symptom free during a winter he spent in a small isolated village in Alaska. No one should be told to change his residence because of bronchiectasis until he has first demonstrated that he will gain the relief he seeks.

Surgery is assuming a more and more important rôle in the treatment of bronchiectasis. Surgical removal of the

affected lobe or lobes is the only ideal measure. Until recently the mortality from the operation was so high as almost to preclude its use. Within recent years improvements in technic have so lowered this that in skilled hands it is no longer prohibitive. It is probable that eventually the operation will become relatively safe. Tudor Edwards has reported a series of 48 lobectomies with a mortality of 8 per cent. At the best there will always be many cases in which it cannot or need not be used.

In unilateral cases phrenicectomy usually produces an appreciable reduction in the cough and sputum and occasionally a symptomatic cure. Why it does this is uncertain. Graham has produced theoretical and experimental arguments tending to prove that paralysis of the diaphragm hinders rather than favors drainage of the dilatations. He cites instances in which the operation seems to have brought on pneumonia and gangrene. In approximately 50 cases, I have not observed this and have had results which lead me to continue using the operation. Recently I have been blocking the nerve and later extracting it if the observed improvement warranted.

Thoracoplasty has been tried and generally abandoned. The cautery lobectomy of Graham has not given good results.

I have chosen 3 cases to present which are unusual enough to warrant consideration and which illustrate certain of the points which I have made concerning the etiology and treatment of the disease.

The first is a case of dry hemoptotic bronchiectasis. This type is of particular interest because it demonstrates that dilatation of the bronchi even in the lower lobes may exist without being complicated by bronchitis and may produce no symptoms. It is also important because it emphasizes the fact that bronchiectasis is a common cause of hemoptysis.

Case I.—Montgomery Ward Medical Clinic of Northwestern University, No. 48,425. Mr. J. P., nineteen years old, first came to the clinic in March, 1932 complaining of coughing and expectorating blood.

His past and family histories were essentially negative. Close questioning failed to reveal any past illness which might have produced dilatation of the bronchi.

His present illness started two years before with a sudden onset of profuse and repeated hemoptyses. He was sent to Edward Sanatorium where Dr. George Dyche made the diagnosis of bronchiectasis and verified it by bronchography. He had remained in the sanatorium four months without further bleeding and had then returned to work. His cough disappeared entirely and he remained free from symptoms until two weeks before coming to the clinic. At this time his hemoptysis recurred and had been repeated frequently during the past few days.



Fig. 134.

Fig. 135.

Fig. 134.—Case I. Dry, hemoptysic bronchiectasis of right lower and middle lobes before injection of iodized oil.

Fig. 135.—Case I. After injection of iodized oil.

Physical examination showed nothing abnormal save decreased breath sounds and occasional coarse bronchial râles at the right base and in the axilla.

x-Rays taken after the injection of iodized oil showed cylindrical dilations of the bronchi in the right middle and lower lobes (Figs. 134 and 135).

On March 18, 1932 the right phrenic nerve was extracted.

Since that time the patient has had no further hemoptyses, but within the past year has developed a slight morning cough. He expectorates about  $\frac{1}{2}$  ounce of sputum each twenty-four hours.

*Case II.*—Extensive saccular bronchiectasis of left lower lobe in boy fourteen years old, secondary to foreign body in nose since childhood. Marked improvement following removal of foreign body, phrenicectomy and postural drainage.

E. M., Montgomery Ward Medical Clinic of Northwestern University, No. 45,492. This boy was fourteen years old when he first came to the clinic in January, 1931. He complained of a chronic productive cough, pain in the chest, hemoptysis and nasal obstruction.

His father had pulmonary tuberculosis.

His mother and 3 sisters and 2 brothers were living and well.

He had measles and whooping cough in early childhood and many acute respiratory infections.

The present illness dated back to infancy. The father said that the boy had always coughed and had a nasal discharge, and has had repeated attacks of pneumonia. For years he had coughed a great deal, severe attacks occurring in the morning and whenever he exerted himself in play. At these times



Fig. 136.

Fig. 137.

Fig. 136.—Case II. Severe bronchiectasis of right lower lobe secondary to foreign body in nostril.

Fig. 137.—Case II. After injection of iodized oil.

he raised large quantities of fetid sputum. His father estimated that he expectorated more than a cupful a day. Slight hemoptyses were common as were also pains in the left chest. Physical examination at that time showed a poorly developed and nourished boy with profuse nasal discharge and frequent loose cough. His complexion was sallow and his attitude listless.

Physical examination showed moderate clubbing of the fingers and dulness, decreased breath sounds and coarse bronchial râles over the lower half of the left lung.

For the x-ray findings see Figs. 136 and 137. x-Rays of the sinuses showed normal aeration.

The patient was given potassium iodide and instructed in postural drainage. The left phrenic nerve was extracted.

He was referred to Dr. O. H. Maclay of the ear, nose and throat depart-



ment, who found a markedly deviated septum, obstruction of the right nostril and mucopus in both sides. A diagnosis of deviated septum with possible foreign body was made.

At operation Dr. Maclay found a metal screw firmly embedded in scar and granulation tissue in the right nostril. The septum was straightened and the tonsils and adenoids removed.

Following these operations improvement was rapid. His cough and sputum decreased markedly and his gain in weight and general health was striking. For the past four years he has coughed only on rising in the morning and has raised less than 1 ounce of sputum each twenty-four hours. Today at the age of eighteen he is a well-developed and alert young man.

In this case it seems certain that the foreign body in the nose and the consequent nasal infection caused the bronchiectasis. That it was important in maintaining the infection in the dilated tubes is evidenced by the prompt improvement following its removal. Much elevation of the diaphragm was prevented by adhesions and it is doubtful if this operation contributed greatly to the result.

Case III.—Severe bronchiectasis of left lower lobe; constant fever; repeated hemoptysis; treatment by medication, postural drainage, phrenicectomy and paraffin pack ineffective; cure following lobectomy.

Miss M. D., Montgomery Ward Medical Clinic of Northwestern University, No. 43,734. This patient, a girl seventeen years old, first came to the clinic in



Fig. 138.

Fig. 139.

Fig. 138.—Case III. Bronchiectasis of left lower lobe before injection of iodized oil. Severe and disabling symptoms.

Fig. 139.—Case III. After injection of iodized oil.

September, 1931. She complained of a chronic cough with profuse expectoration of two years' duration. The onset of her cough was gradual and there was nothing in the family or past histories which could account for it. At the time that it developed she was working in a nut factory shelling nuts, a fact which suggests that a foreign body may have been inhaled. She was raising approximately 4 ounces of fetid sputum each twenty-four hours. Hemoptyses were frequent and fever was present much of the time.

Physical examination revealed a poorly developed and nourished young girl. There were no abnormal physical findings in the lungs.

The x-ray findings are shown in Figs. 138-140.



Fig. 140.—Case III. Following lobectomy. Shadows in right lung field are artefacts.

Postural drainage, phrenicectomy, and medication with potassium iodide were ineffective in improving her condition. She grew gradually worse. Her sinuses which had been normal on admission became infected. In August, 1932 a paraffin pack was inserted over the base of the left lung. This gave no relief.

In November, 1933 the paraffin pack was removed and the left lower lobe resected. Since that time she has gained 12 pounds in weight. Her general health has improved markedly. She still coughs and raises some sputum but has no fever and no hemoptyses. The operation has changed her from a chronic complaining invalid to a healthy and ambitious young woman.

This case is important as demonstrating the severe and disabling type of bronchiectasis. Any procedure, however radical, which offered a possibility of cure was justified. It is of interest that the sinuses became infected three years after the onset of the cough while the patient was under observation.

One could say much more about the details of the treatment. I would say in general that it should be intensive and radical only in proportion to the severity of the symptoms and that in the majority of cases one must be satisfied with partial results. As the mortality of lobectomy is reduced, and I feel certain that it will be, its indications in unilateral cases can be accordingly extended.

In closing I would like to emphasize the importance of cleaning up infections in the upper respiratory tract and the necessity, if this is to be accomplished, of close cooperation with the specialist in diseases of the nose. In our department we had little success from this form of treatment until all of our cases were referred to a single man. Dr. Otis H. Maclay, by frequent consultation with us, has come to understand the problem from our point of view and by so doing has been able to adjust his measures to the requirements of the particular case and to render us invaluable service.

## CLINIC OF DR. VINCENT J. O'CONOR

### WASHINGTON BOULEVARD HOSPITAL

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#### THERAPEUTIC VALUE OF PROSTATIC MASSAGE: WITH A DISCUSSION ON PROSTATITIS AND THE SIGNIFI- CANCE OF PROPER RECTAL PALPATION OF THE PROSTATE GLAND

For discussion this morning I wish to present this patient and give a brief history of his complaint.

A. G., aged thirty-six, came to the hospital complaining of persistent low backache, loss of energy and appetite. He is an unmarried clerk of sedentary habits who has always been well except for occasional sore throats and head colds each winter. He had had measles and scarlet fever in childhood and influenza in 1918. He denies gonorrhea or other urinary infection. He first consulted a physician for sacral pain two years ago. At this time an x-ray was made and the patient was told that he had a "slipped sacro-iliac joint." Orthopedic belts and medicine by mouth did not improve the condition. Several months later he consulted an osteopath who told him he had a "slipped vertebra" but manipulative treatments by him brought no relief. The patient has since taken frequent doses of aspirin and other sedatives with temporary relief. More recently the sacral and lower lumbar pain has been bilateral and when he tries to rise from bed in the morning the effort is most painful. During the day the pain becomes less severe and is often almost entirely absent on retiring at night. Exercise, which he has to force upon himself, does not increase the pain. Other than the above, the pain is not related to bowel movements, urination or any other function. He has very occasional sexual intercourse and thinks the pain is lessened for several days after these experiences.

Physical examination reveals a well-nourished man apparently in good health. The teeth are in good condition, the tonsils appear to be the seat of chronic infection. Heart, lungs, blood pressure and blood count are normal. Urinalysis is negative except for a slight excess of leukocytes (10-15 per high-power field after centrifuging) in the sediment. Mobility of the spine is normal; there are no areas of tenderness along the vertebrae or over the sacrum. x-Rays of the teeth and spine show no abnormality. Rectal examination reveals a normal sphincter, no anal fissure or hemorrhoids and a smooth rectal mucosa. The prostate is twice normal size, soft and boggy without any indurations or infiltrations in the prostatic tissue. The rectal mucosa is

freely movable. Both seminal vesicles are palpable and distended with a somewhatropy consistency on outline. Thorough massage and stripping of the prostate and vesicles is followed by a rapid flow of material at the external urinary meatus and this fluid on cover slip examination under the high-power field of the microscope shows 75 to 100 pus cells per field and many clumps. Cultures and smears of the prostatic secretion show mixed staphylococci and colon bacilli. The day following the diagnostic massage the patient stated that for the first time in two years he had no pain in his back when he awakened in the morning. Our diagnosis in this case is chronic prostatitis of

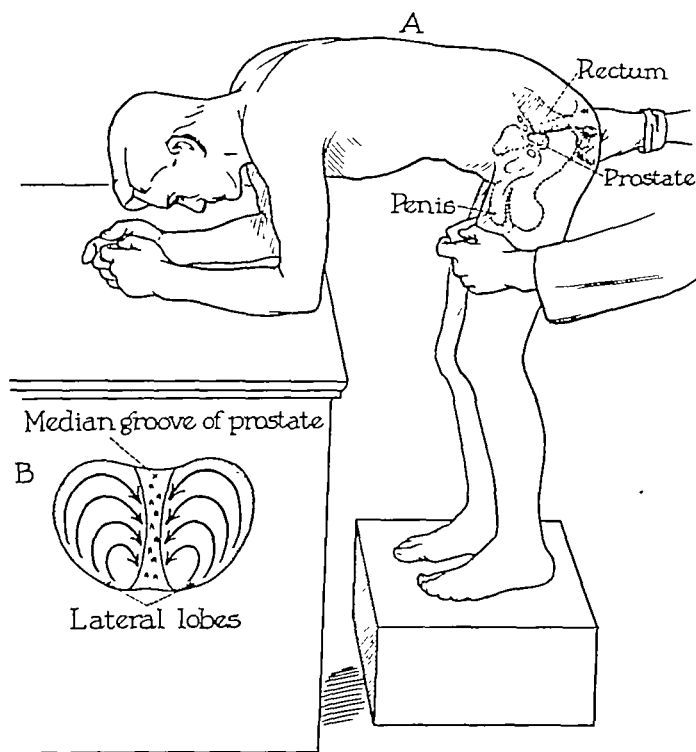


Fig. 141.

nonspecific origin, probably secondary to chronic tonsillitis. The therapeutic procedure will include removal of the tonsils and prostatic massage at five-day intervals until the expressed material yields less than 10 pus cells per high-power field and, of course, until all symptoms are completely relieved.

**Discussion.**—This patient's history illustrates the necessity for a thorough rectal examination of the prostate in every male complaining of backache. Unfortunately the average

physician does not include a routine rectal examination in searching for the cause of complaint in these individuals. This is an omission of which I hope you gentlemen will not be guilty. It is not necessary to be a genito-urinary specialist to make a competent examination of the prostate. The most effective examination may be made with the patient standing on a low stool or platform, the body bent over a table, toes turned in, knees slightly bent, back swayed. If the patient is bedridden, he should be examined lying upon his side with his knees drawn up. The prostate, seminal vesicles, the base of the bladder and the lower end of the ureter may be felt by the examining finger in the rectum. The finger is best protected by a rubber finger cot, using a new one for each examination. A gauze or paper shield for the hand is also discarded after the examination.

Normally the prostate as felt per rectum is heart shaped with its apex toward the anal sphincter, its base more or less notched in the center, the lateral lobes quite elastic, its central groove between the two lobes more or less marked. Normally the prostate does not project into the rectum and the lateral lobes are flat rather than bulging. Careful examination consists in sweeping the tip and flexor surface of the index finger over the surface of the gland and around its borders. All students and physicians should avail themselves of the opportunity to make frequent rectal examinations so that they may learn to differentiate minor or gross changes from the normal.

The lobes of a normal prostate are flat, flaccid and only moderately sensitive. There are no indurations or variations in consistency in the texture of the unaffected gland. Discrete hard masses felt between the rectal mucosa and the prostate proper are usually lymph nodes or phleboliths. Diffuse thickenings within the lateral lobes or projecting toward the seminal vesicles are usually of an old inflammatory nature. Carcinoma most commonly begins in the posterior lobe and the rectal mucosa becomes fixed to the gland which itself becomes immovable. Hard boardlike areas replace the normal prostatic tissue with discrete nodules of cancer to be felt in place

of the smooth, uniform normal consistency. Acute inflammations give the feeling of a tense, hot, swollen gland projecting rectally in an abnormal manner. When abscess occurs in the substance of the gland, an area of softness or fluctuation may be felt. In adenomatous hypertrophy the gland may bulge markedly into the rectum and the lateral lobes, if large, obliterate the median groove, giving one the feeling of a large, smooth, symmetrical tumor.

**Prostatic Massage.**—Prostatic massage first came into popular use in Stockholm in 1894, although several references were made in Germany concerning the cure of chronic prostatitis by repeated digital expression in 1893. The technic most popular with genito-urinary surgeons is as follows:

The patient presents himself with a bladder well filled with urine and he assumes the position previously described. The protected index finger is inserted within the rectum and gentle to firm pressure made first over one lobe and then over the other with a stroking around and downward movement directed toward the openings of the prostatic ducts in the deep urethra. Finally the finger is drawn from above downward over the posterior urethra so as to express secretions from the sinus pocularis and urethral openings of the ejaculatory ducts. This manipulation should be continued for from one to three minutes. Mild massage may be indicated twice weekly; vigorous massage not more often than once a week. The therapeutic benefit derived from digital expression of the prostatic and vesicular content combines the expression of secretion and resultant improved drainage through normal channels, the stimulation of circulation in the region of the prostate proper and increased absorption from infected areas brought about by the above reactions. Rough or too vigorous massage, especially in the presence of acute infection, may force infected material down the lumen of the vas and cause epididymitis.

Prostatic massage is a useful measure in chronic catarrhal prostatitis, in chronic fibrotic prostatitis and in atrophic or atonic conditions of the prostate. It is of no value or is contra-

indicated in acute infections of the prostate, in tuberculosis, neoplasm or hypertrophy. The intelligent treatment of non-gonorrheal prostatitis must include the removal of systemic foci of infection, such as abscessed teeth, infected tonsils, nasal sinusitis, etc. Stricture of the urethra, when associated, must be treated by progressive dilatation of the urethra, but preferably at an interval of two to three days between prostatic manipulations. Rectal insuffusion of heat, systemic stimulation of immunity, proper hygienic advice, and urinary antiseptics may be combined to good advantage with regular prostatic massage in the treatment of chronic prostatitis.





## CLINIC OF DR. RICHARD J. TIVNEN

### MERCY HOSPITAL

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#### THE VALUE OF EYE SYMPTOMS IN THE DIAGNOSIS OF GENERAL DISEASE

**Preliminary.**—The physician's greatest problem is diagnosis. His chief reliance in establishing it is the symptoms the patient presents. It is exceptional for one symptom alone—the so-called pathognomonic symptom—to determine a diagnosis. Practically always one must depend upon a group of symptoms in reaching a conclusion. Clinical experience demonstrates that the largest yield of diagnostic data results when one adopts as a routine in every case a comprehensive plan of procedure, which interrogates, so to speak, every organ or structure, which offers a possibility of contributing to the diagnostic problem. The value of eye symptoms in the diagnosis of general disease is of interest in this connection.

Eye symptomatology is of frequent aid, not alone in diagnosis of general disease, but is often also of great value in the *early* diagnosis and prognosis, notably in such general conditions as Bright's disease, brain tumor, arteriosclerosis, diabetes, and endocrine disturbances. A field offering such a yield of diagnostic and prognostic data should not therefore remain unexplored in general examinations. It is not unusual, however, to hear of patients who have been given what is popularly referred to as a "check-up" and no investigation of the eyes has been included in this general examination. Many personal experiences might be cited demonstrating the unwisdom of such a course of procedure. I recall the case of a young child who had been given such a "check-up" by a very capable pediatrician which did not include an eye investiga-

tion. The little patient was given a clean bill of health and the alleged backward tendencies which prompted the examination were ascribed to the mother's solicitude and anxiety. A later examination of the patient's eyes disclosed the presence of congenital cataracts. Another instance of a young child whose "check-up" in which an eye investigation was omitted, resulted in the diagnosis of "gastro-intestinal disturbance;" a subsequent eye examination disclosed choked disks and the diagnosis of brain tumor.

Many reasons may be assigned in extenuation for the omission of an eye investigation as a routine in general examination. Chief among these reasons perhaps is that the usual undergraduate medical training does not ordinarily emphasize the value of eye symptoms in the diagnosis of general disease and usually but relatively little time in the medical curriculum is devoted to training in the use of the ophthalmoscope and other ophthalmologic technic. After some considerable experience in teaching in the field of ophthalmology, I hold the strong conviction that a student may with relatively little expenditure of time, training, and a negligible outlay for equipment perfect himself to a degree that he may may with confidence conduct a character of eye examination which will prove of the greatest value to his patient and of immense satisfaction to himself.

As a preliminary, it is of interest to refer to an unusual phenomenon which is associated with many eye diseases. Inflammation of body structures generally are usually manifested by pain, redness, edema, swelling, etc., and the function of the part is more or less impaired. This does not hold true for many serious eye inflammations, especially lesions of the deeper eye structures. It is quite common, for example, for a patient to be affected by such destructive eye inflammations as optic neuritis, retinitis, choroiditis and choked disk, and the external appearance of the eye be quite normal, the patient experiencing no pain whatever and his vision manifesting little or no impairment. It is a grave error, therefore, to accept either the normal appearance of the eye, the lack

of the patient's complaint of impaired vision or of pain or distress of the eye as an indication that there is no active pathology present in these deeper structures. An examination of these deeper parts with the ophthalmoscope is the only safe method of discovering this hidden pathology. It is also true that many general diseases during their course attack the eye so regularly and so consistently that the eye symptomatology of these diseases should be listed among their regular general symptomatology instead of being regarded and referred to as "complications."

It may be of interest to outline briefly the various tests and technic used in conducting an eye investigation.

#### EXAMINATION OF EYES

1. **Eye History.**—A special eye history should always be obtained in addition to the general history. If glasses are worn, it should be ascertained why they were ordered and the results of their use.

2. **Inspection of the Eyes.**—This is the first test made. The patient is placed in good daylight illumination and a general survey is made of his eyes. The main features to be noted are first, changes affecting the eye appendages, lids, tear channels, etc., such as edema or inflammation of lids, drooping of lids (ptosis), inability to close lids, arrangement of eyelashes, eye discharge, lacrimation, inspection of lacrimal puncta, tear ducts and lacrimal sac, eversion of lids to determine condition of conjunctiva, photophobia; next the eyeball itself—if it be reddened, its position, if prominent (exophthalmos) or sunken (enophthalmos), or if one eye deviates (strabismus, paralysis, etc.); finally testing for gross impairment of globe movements is made by holding a finger in front of patient's eyes and directing him while keeping head still to follow its movements in various directions; if binocular movement is normal both eyes should follow equally without lagging the movement of the finger in all directions; also the testing the lid movements, openings and closure, including the various lid signs detailed under Exophthalmic Goiter. The

examination of the cornea, pupils, etc., is best carried out with special tests to be referred to later.

3. **Test of Vision (Visual Acuity).**—In all tests of vision, each eye is tested separately and the eye not being tested is covered, but not pressed down. If glasses are worn, vision should be taken without and with them. Vision is tested for *distance* and for *near* (reading distance).

*Test for Distance Vision.*—For this purpose a large card upon which is printed letters of various sizes arranged in lines

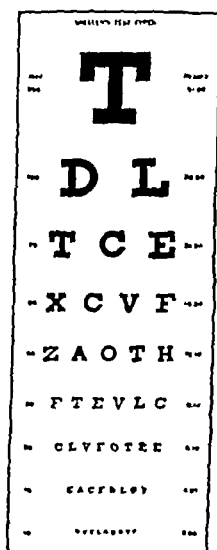


Fig. 142.—Test of vision: Tests for distant vision—Snellen's test types.

is used, called *Snellen test types* (Fig. 142). Each line of letters is marked by a number above the line. The card is hung on the wall at a distance of 20 feet from the patient and on a level with his eyes, care being taken that the card is well illuminated. The distance of 20 feet is determined upon because rays of light emanating from objects at that distance are practically parallel and a normal eye requires no accommodation effort in bringing parallel rays to a focus; it is in a state of accommodative rest. The line marked 20 is therefore accepted as the standard of normal distant vision. If the

patient can read all the letters of this line at a distance of 20 feet, his vision is normal and it is recorded as a fraction  $\frac{20}{20}$ , the numerator indicating the distance the patient is from the card; the denominator the number of the line read.

Should the patient be unable to read the normal vision line—20—, he reads then the smallest line of letters he is able and the result is recorded similarly by the fraction as above. If he is unable to read the top line of letters on the chart marked 200, he is directed to approach the chart and stop when he is able to read the top line, his new distance from the chart is then estimated and if it be, for instance, 10 feet, his vision is recorded as  $\frac{10}{200}$ , the numerator—10—indicating the new distance he is from the card, the denominator—200—the line he is able to read. If he cannot read the top line marked 200 at any distance, he is directed to count fingers held a short distance in front of eye and the result is recorded as for example, "Counts fingers at 2 feet." Should he not be able to count fingers, his perception and projection of light is tested. This test is made in a dark room, the patient seated, an electric wall or floor light being behind him. He is directed to look directly forward and hold his eye perfectly still throughout the test. The examiner stands directly in front of the patient and with his ophthalmoscope reflects light into the patient's eyes from various angles, aiming in so doing to test the functional integrity of the center and the extremes of the retinal periphery. The patient is directed to say "now" the instant he sees the light, this indicates his *light perception*; then he is directed to reach out with his hand and touch the source of the light (the ophthalmoscope), this indicates his *light projection*. If he is wholly unable to "perceive" the light, the eye is blind. If he is able to perceive "the light" but is unable to "project" it (locate its source) accurately, this result is recorded as "perception—present; projection—poor" (or other qualifying phrase that clearly indicates the condition).

Test types are also usually marked with the metric scale, 6 meters being the equivalent of 20 feet, and  $\frac{6}{6}$  being the

equivalent of  $\frac{20}{20}$ . Most cards also state after each line the percentage of normal vision the line represents. Where a distance of 20 feet is not available it may be obtained by the use of a mirror, the test type being placed behind the patient and the letters reflected into the mirror hung on the wall opposite the patient. There is also a visual testing apparatus on the market which enables one to test vision at any distance. When the patient is an illiterate, a card is used with the letter E placed in different positions, the patient being

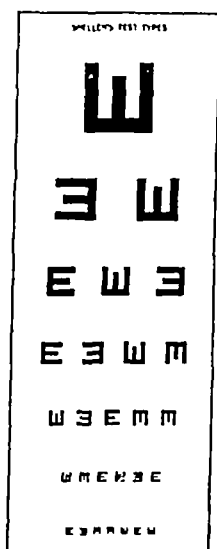


Fig. 143.—Test types for illiterates. (May, "Diseases of the Eye," Courtesy of William Wood and Co.)

directed to indicate by his hand the direction of the arms of the E (Fig. 143). The symbols for recording vision may be either those of the Latin words, "*oculus dexter*" abbreviated to the symbols, O.D., or its English equivalent, R.E. (right eye) and "*oculus sinister*" abbreviated to the symbols, O.S., or its English equivalent, L.E. (left eye) or "*oculus uterque*" abbreviated to the symbols O.U., or its English equivalent, B.E. (each or both eyes). The complete formula for recording the vision should, for example, read:

*Vision*O.D. (or R.E.)  $20/20$ O.S. (or L.E.)  $20/40$ 

*Test for Near Vision.*—For this test a small printed card upon which is printed a series of paragraphs in different size type is used, called *Jaeger's test types* (Fig. 144). Each

**No. 1.**

Engaged in manual occupation of a minor sort, the laborer has little opportunity either to try or to measure his eyes; his sight, when attacked by local inflam-

**No. 2.**

matory diseases or the consequences of constitutional disorders, remains good, though its acuteness lacks that extreme development

**No. 3.**

which follows abundant use in higher types of occupation. But with the literary worker it is differ-

**No. 4.**

ent: keeping pace more or less with mental activity, the eye is constantly called upon for

**No. 5.**

action, in reading for information and reference on the one hand, in recording the

**No. 6.**

fruits of such occupation on the other. Observation has shown that deteriora-

**No. 7.**

tion in eyesight and changes in the form, and hence in the dioptric

Fig. 144.—Test for near vision—Jaeger's test types. (May, "Diseases of the Eye," Courtesy of William Wood and Co.)

paragraph is numbered. The patient with the card held at the usual reading distance (10 to 13 inches) is directed to read the smallest type paragraph he is able to read and the result is recorded for example, as: Reading = Jaeger —No. 2.

**4. Visual Field Tests for Form and Color.**—A satisfactory method of disclosing gross changes in the visual form field is as follows: Patient and examiner are seated near to and exactly opposite each other. To test the patient's right



eye for a field of vision, the patient covers his left eye, the examiner his right eye; each looks directly and steadily at the other's open eye throughout the test. The examiner then extends his left arm, with fingers spread apart, to his extreme left in the horizontal plane and slowly brings the fingers inward midway between the patient and himself. The patient is directed to say "now" the instant he sees the advancing fingers. The examiner uses his own recognition of the advancing fingers to check the patient's responses; a marked discrepancy between the two is evidence of impairment of the visual field in the meridian tested, in this case the temporal field. The nasal field is similarly tested by the examiner extending his right arm and slowly advancing them to his left with fingers spread to his extreme right; likewise the upper and lower fields by alternately advancing the fingers from the extreme upward position, downward and then from the extreme downward position, upward, the directions to the patient being the same as in the first instance. The patient's left eye form field of vision is tested in the same way, the patient covering his right eye, the examiner his left. The color fields also may be tested in a similar way using small squares of colored paper suspended between the points of a writing pen. For more refined tests of the visual fields it is necessary to employ the perimeter, campimeter or the various screens.

**5. Testing the Tension of the Eye.**—This is quite satisfactorily done with the fingers. The patient is directed to look downward and to avoid "squeezing" the lids. The examiner then places the tips of the index finger of each hand upon the closed upper eyelid, approximately just back of the corneal periphery and gently dimples or palpates the underlying eyeball and thus obtains information of its degree of hardness or softness. The tension of the fellow eye is the standard for comparison (Fig. 145). The symbols used for recording the findings are: T= meaning tension; the letter N= meaning, normal, and the signs plus + and minus —, used as follows:

T=n = normal tension.

T+1 = appreciable hardness.

T+2 = decided hardness.

T+3 = stony hardness.

T- = diminished tension.

T-1 = appreciable softness.

T-2 = decided softness.

T-3 = very soft.

For more exact tension estimates the tonometer is used.

## 6. Oblique Illumination Test (Lateral or Focal).—

This test supplies information of eye structures which occupy



Fig. 145.—Testing of tension. (May, "Diseases of the Eye," Courtesy of William Wood and Co.)

the area from the cornea to the depth of the anterior portions of the vitreous, viz.—the cornea, the anterior chamber, the iris, the pupil, the lens and anterior portion of vitreous. Dilating the pupil will enable one to study more minutely the presence of iris adhesions to the anterior capsule of the lens (anterior synechiae), the lens and the forward portion of the vitreous. For more accurate examination of the lens and vitreous, however, the *direct illumination test* is necessary. The oblique illumination test requires 2 convex lenses of 2–3 inch focus; it is more convenient to use a loupe in place of

the magnifying lens. The test should be conducted in a darkened or better a dark room (Fig. 146). The light is placed approximately 18 inches to the side of and slightly in front of the patient and on a level with his eyes. The examiner adjusts the loupe to his own eyes, holds the focusing lens at its rim with the thumb and index finger, applies his little finger to the patient's face to steady it, and concentrates the light on the patient's cornea. The focusing lens should not be tilted, but its surface should be at right angles to the light. For examination of the cornea, anterior chamber and iris, pupil and anterior portion of lens, the light is concentrated

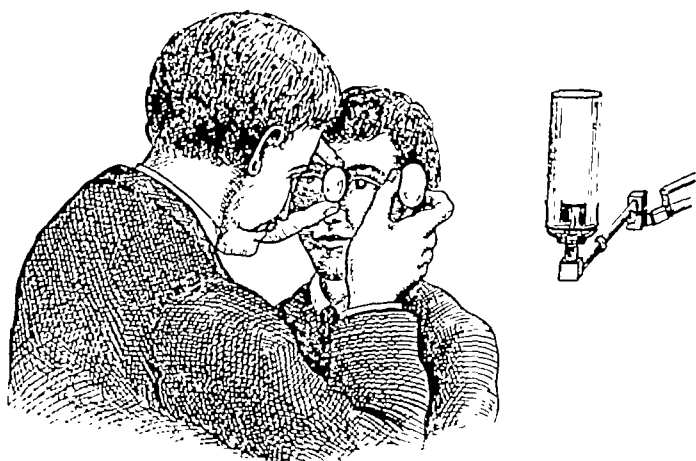


Fig. 146.—Method of oblique illumination. (deSchweinitz.)

on these structures in an oblique direction; for investigation of the central and posterior areas of the lens and forward portions of the vitreous its incidence should approximate the perpendicular. For identification of minute foreign bodies in the cornea, iris or lens or fine opacities of cornea or lens a lessened illumination or utilizing the edge of the concentrated light is more useful. The reactions of the pupil may also be investigated with this test, but they are perhaps better included in the special test of the pupils.

**7. Pupil Tests.**—These tests should be carried out in a dark room. They determine the pupil equality, its regularity

of outline, size and reactions. The reaction tests are three, direct light, consensual and accommodation convergence. The *direct light reaction* is made by alternately reflecting light—either with the focusing lens or the ophthalmoscope on and off the pupil and noting its response; the *consensual* reaction is tested similarly, except the reaction of the unilluminated eye is observed; the *accommodative convergence reaction* is obtained by holding the fingers in the midline close to the eyes and noting both the convergence of both eyes and the associated pupillary contractions, as the fingers are brought



Fig. 147.—Direct illumination. (Curt Adams.)

close to the eyes. The clinical value of these pupillary tests is important and they should be made as a routine in all examinations.

**8. Direct Illumination Test.**—This test is made by reflecting light into the eye with the ophthalmoscope used either with the aperture or any convex lens desired, held approximately a foot from the patient's eye (Fig. 147). It is used to ascertain the condition of the media—the cornea, aqueous, lens and vitreous; opacities in these appearing as black or dark spots: if the patient be requested to move the eye quickly

in various directions and suddenly halt its movement, floating opacities in the vitreous, as dark spots, will float by the illuminated pupil.

**9. Ophthalmoscopic Test.**—A good electric ophthalmoscope is required (Fig. 148). The direct method is satisfactory for the usual examination; it gives a magnification of 15 diameters and presents the eye structures in the upright or natural position. It is usually necessary to dilate the pupil to obtain a satisfactory view. For this purpose either cocaine—4 per cent solution or euphtalmine—2 per cent solution or homatropine—2 per cent solution is used; 2 to 3 drops of



Fig. 148.—Use of ophthalmoscope—direct method. (May, "Diseases of the Eye," Courtesy of William Wood and Co.)

solution instilled at five-minute intervals being usually sufficient, the eyes remaining closed during the period of instillation to avoid drying the cornea. The tension should always be taken before the mydriatic is used and if it is elevated a mydriatic should be omitted. Following the use of the mydriatic, as a routine, 2 or 3 drops of eserine sulphate,  $\frac{1}{4}$  per cent solution, should be instilled at five-minute intervals to secure contraction of the pupil as a precaution against inaugurating a glaucoma.

**Examination of the Eyegrounds.**—There are four elements one must identify in examining the eyegrounds: The

*optic disk* (optic papilla); the *macula*; the *retinal vessels* and the *general fundus* (Fig. 148a). Obtaining simply a general or "panorama" view of the eyegrounds as a whole is not sufficient. Each of the four elements or components above mentioned must be studied individually.

*The Optic Disk.*—This is the first element identified, it is a "landmark," so to speak; it is the point of entrance of

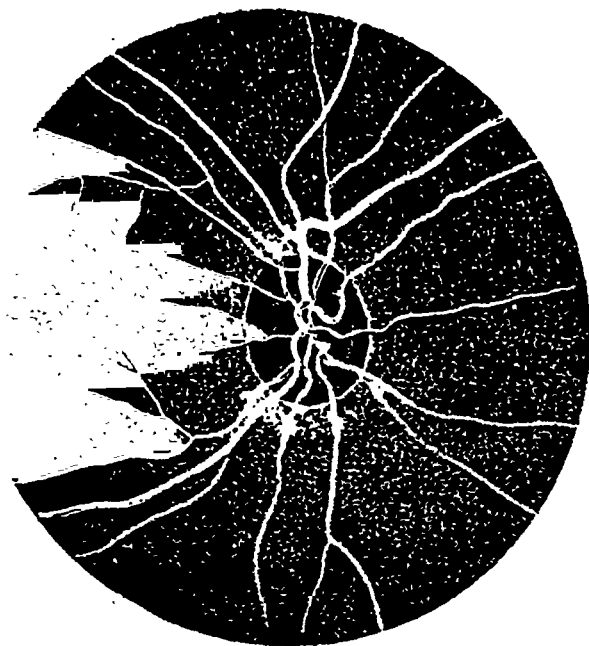


Fig 148a—Normal fundus of the uniform stippled type. The papilla is oval, has sharply defined margins; is normal in color; the pigment epithelium is concentrated about the papilla and in the region of the macula. The dark, larger vessels, without distinct light streaks are the veins; the bright, narrower ones, with distinct light streaks are the arteries. (Adam Foster, "Ophthalmic Diagnosis.")

the optic nerve in the eye and hence is often referred to as the nerve head: it is also the physiological "blindspot"; the disk is located slightly nasal to the posterior pole of the eye; its form is circular or oval, pale pink in color, though this varies in degree depending upon the pigmentation of the gen-

eral fundus, is usually paler on its temporal side, its margins are well defined and two rings usually surround it—a white inner ring, the scleral, and an outer dark ring, the choroidal; on its temporal side a funnel-shaped excavation is commonly seen, the vascular funnel or physiological cup, caused by the separation of the nerve fibers, at the bottom of which may be seen the stippled gray dots of the lamina cribrosa (Fig. 149). The chief features concerning the optic disk to be noted are

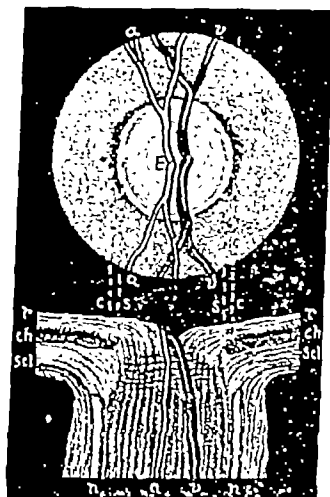


Fig. 149.—Ophthalmoscopic view and longitudinal section of the disk. *a*, Central artery; *v*, central vein; *E*, physiological excavation; *s*, scleral ring; *c*, choroidal ring; *r*, retina; *ch*, choroid; *scl*, sclera. (May, "Diseases of the Eye," courtesy of William Wood and Co.)

its color, the definition of its margins, changes in its surface and its level (swollen, etc.) compared with surrounding retina.

The *macula* (*macula lutea*—yellow spot) is located approximately two disk diameters to the temporal side and a little below the horizontal meridian; it is identified as a rather oval ring, its long axis horizontal; a bright red spot at its center is the fovea centralis. Slight pathologic changes at the macula interfere seriously with vision—it therefore should be inspected with exceeding thoroughness.

*The Retinal Vessels.*—At the disk the central vessels, artery and vein, divide into a main upper and lower branch and these again branch into temporal and nasal branches; the arteries are smaller, redder, run a straighter course, and their light streak is more defined than the veins; the veins are larger, darker, course more tortuous, light streak not so defined as the arteries; arterial pulsation is uncommon and probably pathologic; venous pulsation especially on the disk is not infrequent and is probably not pathologic; there is no consistency in the matter of vessel crossings, a vein may cross an artery or an artery a vein; an artery, however, never crosses an artery, nor a vein, a vein. The light streak of the arteries divides the vessel into two red lines; normally the walls of the vessel itself are transparent and cannot be seen, hence the red lines observed represent the column of blood in the vessel and not its walls. The important features of the retinal vessel to be noted are, the relative size of arteries and veins, variation in their caliber, undue tortuosity, changes in their walls, interruptions in the blood current, hemorrhages along their courses, and pulsations.

*The General Fundus.*—The general appearance of the fundus is due to the red reflex of the vessels in the choroid and this appearance varies depending upon the amount of pigment in the choroid itself and in the retinal pigment layer. Examination of the eyegrounds of blondes, brunettes, negro, mulatto and albino will familiarize one with these varied appearances.

The above described eye tests are definitely within the scope of the general physician and may be carried out during the general examination with a relatively small expenditure of time and effort. Necessarily the interpretation and clinical application of the findings will require some further study and investigation. This may be done by consulting one of the many excellent small volumes on medical ophthalmoscopy, supplemented by practice in the use of the ophthalmoscope on the schematic eye, equipped with colored disks illustrating the normal and pathological eyegrounds.



We will now discuss more or less briefly a few diseases in which eye symptomatology is a rather frequent feature, which will serve to emphasize the diagnostic value of eye symptomatology in general disease.

#### HEADACHES—EYESTRAIN

Headaches are one of the most frequent and distressing maladies which usually come first for relief to the general physician. Very many headaches may properly be classified as eye symptoms, especially those chargeable to "eyestrain." These so-called "eyestrain" headaches are due to a variety of ocular causes, such as refractive errors, particularly hypermetropia, low grades of astigmatism, fatigue of the ciliary muscle, muscular imbalance, etc.

The recognition of the possibility of headache being due to eyestrain is, therefore, a matter of interest and concern to the general physician. There are a number of special features commonly associated with eyestrain headache which strongly suggest the likelihood of the eyestrain being the cause of the head distress. These special features may be briefly summarized as follows:

The *location* of the headache is not always as one might expect a helpful diagnostic aid; any area of the head may be attacked; it is, however, quite usual to have it referred to the region of the eyes—mid, supraorbital, or frontal, and quite commonly to the region of the occiput; headaches provoked by use of the eyes, notably unusual eye demands, such as "shopping," "theater," "motoring," "embroidering," are of especial significance; the time of onset, while suggestive, is not a dependable factor, even the so-called "waking headache" which appears after a good night's rest is often found to be an "eyestrain" headache, due to the fact that on awakening the accommodative function is called into instant and abrupt use and it is this accommodative strain and fatigue which plays the major rôle in headache due to eyestrain. Other suggestive factors are such "asthenopic symptoms" as blurring of vision, irritation and burning of eyes, spots before eyes,

redness of lids, blinking and lacrimation, photophobia, inability to continue sustained use of the eyes without a feeling of fatigue or strain. Very frequently sufferers from low degrees of refractive errors complain of symptoms such as vague, ill-defined headaches which completely disguise the origin of their difficulty as being due to eyestrain. A characteristic of this class of cases is that seldom do they associate their headaches and other symptoms with their eyes and few of them have impaired vision. There are other very serious eye and general diseases in which headache is commonly an outstanding symptom. One of the most destructive of eye diseases, viz., acute inflammatory glaucoma, is the cause of severe headaches and since its tendency is to rapid involvement of sight, its early recognition is paramount for conservation of vision. Fortunately, as a rule, in this disease suggestive eye symptoms, such as foggy vision, redness of the eyeball, pain in the eye itself, dilatation of the pupil, and especially increase of the intraocular tension are associated with the headache and direct one's attention to the eye as being its cause. It should be noted, however, that often in the early stages of glaucoma, the so-called "prodromal stage," these suggestive eye symptoms are often absent. These "prodromal types" should be kept strongly in mind; they are frequently only diagnosed by a very searching eye investigation. In the other variety of glaucoma—the noninflammatory type, the so-called chronic simple glaucoma—the patient may not complain of severe headache, but only, perhaps, of a vague, rather ill-defined head or eye distress and the eye exhibits no inflammatory signs, but is normal in appearance. This type of glaucoma is an insidious, destructive eye disease, common in elderly people and requires, as a rule, thorough repeated eye examinations to exclude it.

Headache usually of a severe type is also often an outstanding symptom of brain tumor. The familiar symptom triad of headache, emesis and vertigo should always arouse a suspicion of brain tumor. Examination of the eyegrounds should always be done in such cases; it frequently discloses

the characteristic eye symptoms of brain tumor, viz., optic neuritis or choked disk.

**Practical Eye Diagnostic Summary.**—In all patients suffering with headaches of any form, severe, vague or ill-defined, the eyes should be investigated. The presence of normal vision, the normal appearance of eyes as well as absence of complaint of direct eye symptoms, does not rule out the possibility of the eyes being accountable. In elderly patients, particularly, glaucoma is the important eye disease to exclude and since increase of tension is the outstanding symptom of glaucoma, the tension should be taken as a routine in all patients. Low grade refractive errors, astigmatism, hypermetropia, are the cause of a large number of headaches and therefore the refractive condition of the eyes should be determined. A persistent headache should always suggest brain tumor, and an eyeground examination should be made for confirmation.

#### EXOPHTHALMIC GOITER

(Parry's Disease; Graves' Disease; Basedow's Disease)

A great number of eye symptoms or signs have been described as associated with this disease. Among them the following may be enumerated. Exophthalmos, von Graefe's, Dalrymple's, Stellwag's, Moebius', Kocher's, Gifford's, Suker's, Jellinek-Teillais', ophthalmoplegia, etc. Of these, there are six symptoms, exophthalmos, von Graefe, Dalrymple, Stellwag, Moebius, Gifford, which are relatively constant and are commonly accepted as being a part of the symptom complex of the disease. For clinical purposes, and without regard for the various theories assigned as causal factors in their production, I have found it of advantage to group these seven symptoms or signs in the following manner: *One* of them, the *exophthalmos*, concerns the *position* of the eyeball; *four*, the *von Graefe, Dalrymple, Stellwag, and Gifford*, concern the *eyelids*; *one*, the *Moebius*, concerns the *movement* of the eyeball (convergence, etc.). These may be discussed briefly as follows:

**Exophthalmos.**—Exophthalmos, when apparent, is the most striking symptom of Graves' disease and is the symptom from which the term, exophthalmic goiter, usually applied to the disease originated.

In the earlier studies of the disease the "tripod" of symptoms—exophthalmos, tachycardia and thyroid enlargement—were regarded as the "diagnostic syndrome" of Graves' disease. More recent clinical research has altered and amplified this concept. The symptom of exophthalmos, however, is still regarded, with such reservations as these later researches have suggested, as an important part of the symptomatology of the disease. Formerly, it was believed that exophthalmos was an invariable accompaniment of the disease symptomatology. At present it is said to be absent in atypical cases—the so-called *formes frustes* types. Bram believes that "exophthalmos occurs sooner or later in from 65 to 85 per cent of subjects of Graves' disease."

In addition to the term, "exophthalmos," the symptom—depending somewhat upon its degree—is often described as a "bulging" or "prominence" of the eyes; also as "pop-eyes," "goggle-eyes," "proptosis," etc.

The malposition of the eyes is straight forward, the degree of prominence varying from slight protrusion, at times difficult to estimate, to extreme protrusion interfering with lid closure, the latter condition exposing the eye to the grave danger of corneal ulceration, panophthalmitis, possibly loss of the eye.

The mobility of the eye is rarely impaired to any considerable degree. These two characteristics—the straight forward proptosis and the retention of practically normal mobility of the eyeball, are of considerable value in differentiating from an exophthalmos due to orbital or nasal accessory sinus pathology.

Both eyes are usually involved. A difference in degree between the two eyes is frequent, notably in the early stages of the disease; only one eye may also be affected, the other appearing normal.

Willebrand and Saenger report that in one-seventh of the cases the exophthalmos is unilateral or is larger on one side. It is generally regarded as the first *eye* symptom to appear, though in the majority of cases it is a late manifestation occurring subsequent to the other general manifestations, and persisting—possibly the last symptom to disappear. Its onset is more or less insidious and its evolution as a rule gradual. In certain cases, however, in which such factors as violent freight, emotional excitement, etc., are profound, its onset may be abrupt. Falta, for example, states that exophthalmos may even come on in one night or in a few days; Dock, that “it may come in in a few days or even minutes, but usually does so slowly, sometimes irregularly.” Apparently there is no dependable ratio between the degree of the exophthalmos, its distribution—mono- or binocular—in relation to the thyroid enlargement and the intensity of the general symptomatology.

The various views assigned as etiologic factors in the production of the exophthalmos are summarized by Fuchs as follows: (a) Engorgement of the orbital vessels; (b) irritation of the sympathetic causing tonic contraction of the unstriated muscle fibers running in the orbit from the equator of the eye to the orbital septum (Landstrom); (c) to the accumulation of fat in the orbit with edema of the ocular muscles (Foster Moore); (d) to suprarenal insufficiency (Shapiro and Marine). Plummer and Wider in an extended review of the subject state: “The vast amount of clinical evidence still indicates that the immediate cause of exophthalmos in exophthalmic goiter is closely linked with actual changes in the function and pathology of the thyroid gland.”

It is to be noted that exophthalmos often occurs independent of endocrine difficulties, notably in corpulent individuals, patients with high myopia and those afflicted with anatomical peculiarities such as “tower skull” (Thurmschädel), lack of tone of the recti muscles, orbital and nasal accessory sinus disease, and aneurysm. It has also been reported as occurring in chronic nephritis.

Various instruments are in use to measure the degree of exophthalmos—the exophthalmometer, statometer. Probably as satisfactory a means is to apply a straight edge vertically to the upper and lower orbital margins, the lids being closed. This edge, thus applied, in the normal position of the globe should just press gently upon the apex of the cornea through the closed lids.

**von Graefe's Sign.**—Normally the upper lid covers the same ratio of the cornea in the upward and downward movements of the globe and no portion of the sclerotic coat is visible. In the von Graefe sign as the eye is directed downward the upper lid does not follow it perfectly but lags behind with the result that a varying amount of sclera is exposed. The sign is elicited in the following manner: An object is held in front of and slightly below the patient's eye and he is directed to follow its movements without movement of his head. The object is then *slowly* moved downward and if the von Graefe's sign be present a varying rim of sclera will be seen between the upper margin of the cornea and the lower margin of the upper lid. Occasionally also, as the eye is moved in the upward direction the upper lid proceeds more rapidly than the eyeball, an impairment of synchronous function will become evident, possibly in the form of a "jerking" of the upper lid.

Solomon Solis-Cohen (referred to by Bram) describes what he terms the "hitch sign" of the upper lid which he considers the larval form of von Graefe's sign as follows: "When the eyelid begins its downward course over the eyeball it stops short (the 'hitch'), then proceeds downward to complete its descent. When the lid is again raised it does so with a continuous movement, but presents a sudden hesitancy or 'hitch' in its upward course." von Graefe's sign while an important eye sign of Graves' disease may be entirely absent, be unilateral though usually involving both eyes, may fluctuate, and apparently exhibit no dependable association with the goiter itself or the exophthalmos. It is said, however, to appear as an earlier eye manifestation and persists longer than the exoph-

thalmos. Reports as to the incidence of the symptom vary from 15 to 55 per cent.

Sharkey (referred to by Foster Moore) states that the symptom is not limited to Graves' disease but that of 613 cases of all kinds of disease, excluding Graves', it was present in 12 cases and that many people can produce it voluntarily.

Willebrand and Saenger (referred to by Dock) give five theories of the cause of the symptom, viz.: Sympathetic; central; action of the orbital vessels upon the levator; insufficiency of the orbicularis; increase of the forces which cause elevation.

**Dalrymple's Sign.**—This sign consists of a retraction of the upper lid with consequent widening of the palpebral fissure, the sclera being exposed above and below the cornea. This produces in the patient the so-called "*look of fright*" or "*staring expression*." According to Dock, "it occurs early, is rarely absent, varies from day to day and sometimes is more distinct on one side." This sign is also found in hysteria, tetanus, pregnancy, and in maniacal maladies. Its cause is attributed to spastic contraction of the musculus tarsalis superior due to irritation of the sympathetic (Fuchs).

**Stellwag's Sign.**—This sign consists of a diminished frequency of winking. Normally the function of winking distributes the lacrimal fluid over the cornea, bathes it, clears the cornea of dust and prevents the corneal layers from drying. Winking takes place normally, approximately three to ten times per minute; in Graves' disease it may not take place more than once in several minutes. Interference with this corneal protective function exposes it to irritation and infection. It is not uncommonly an early symptom and is said to occur in 30 to 50 per cent of cases.

**Moebius' Sign.**—This sign is a reduction in the convergence function not attributable to muscular paralysis or exophthalmos.

**Gifford's Sign.**—In this sign difficulty is experienced in everting the eyelid, and is regarded as of frequent occurrence.

The foregoing résumé of the ocular manifestations of

Graves' disease emphasizes the value of these symptoms to the clinician as aids in the diagnosis and in estimating the clinical progress of the disease.

**Practical Eye Diagnostic Summary.**—In all cases of suspected exophthalmic goiter, the eye and its appendages should be examined. The eye symptoms exhibited concern mainly the position of the eyeball, lid movement and convergence. The various impairments of these—referred to—should be investigated in a detailed way in every case.

### ARTERIOSCLEROSIS

In November, 1931 a patient, aged fifty-nine, consulted me for change in reading glasses; no general complaints; considered himself to be in excellent physical condition. Examination of the eyegrounds disclosed an arteriosclerosis of the retinal vessels of marked degree. He was advised to have a general physical examination. Within the following four months the patient was given a thorough general physical examination in two different outstandingly recognized clinics. The findings of both clinics, other than hypertension of moderate degree, were negative. Approximately five months later the patient while attending a hockey game was stricken with cerebral hemorrhage from which he later died.

According to Fraser's survey of life insurance mortality experience for the year 1934, "the mortality from the cardiovascular-renal group (a group that includes heart disease, chronic kidney disease, apoplexy, and arteriosclerosis) far outweigh those from any other cause."

The sequential relationship of hypertension, arteriosclerosis, the cardiovascular-renal group of diseases, and vascular cerebral pathology, is, as yet, undetermined. Whatever the final verdict may be, it is exceedingly probable that arteriosclerosis will occupy a prominent place in the final estimate. As Osler well says, "the tragedies of life are largely arterial," and one may add, arteriosclerosis plays a major rôle in their enactment. Early recognition of a beginning arteriosclerosis is therefore of outstanding value in conserving life. The retinal vessels, in common with other general vascular structures share in the attack of sclerotic processes; often they present evidences of such invasion before it is manifested in other portions of the body. It is not too much to say that no part of the body offers a more fruitful field and relatively easy



method of obtaining reliable data concerning the condition of vascular structures than that offered by the retinal vessels and fundus. Numerous observers confirm this view.

Osler, for example, states, "Of all the vessels in which to see early thickening, the retinal arteries are the most impor-

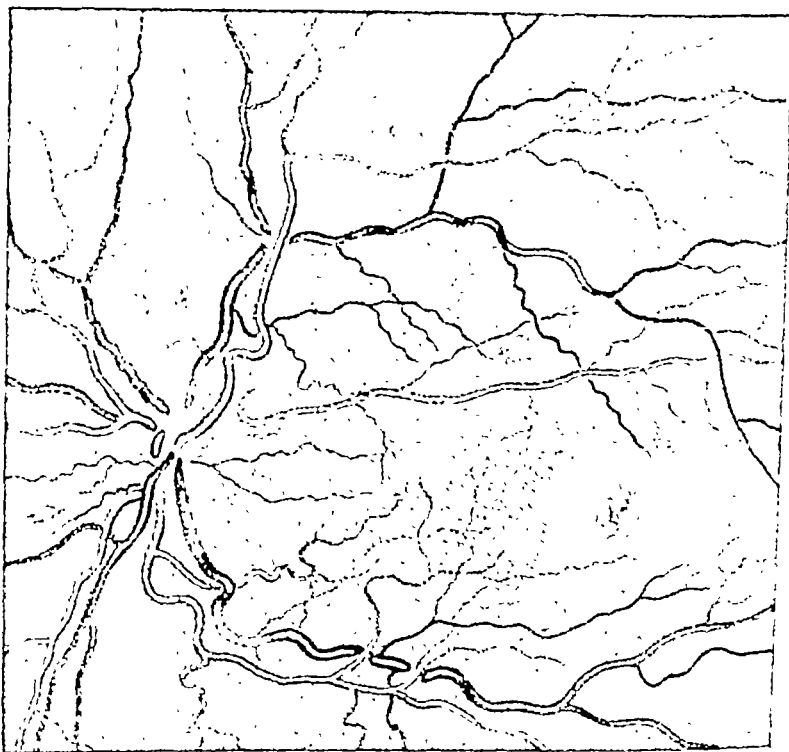


Fig. 150.—A case of arteriosclerotic retinitis. From a woman aged sixty-five, whose systolic blood pressure was greater than 300 mm. She died of "a stroke totally blind" four years and four months after the drawing was made. The arteries are very bright, the lower one showing a dotted reflex, and when seen three years and one month later many of them were converted into fibrous threads. The veins are deeply cut into by the arteries; in one place a vein rides over a thickened artery. A few hemorrhages and a number of the discrete dots of arteriosclerotic retinitis are seen. The disk edges are blurred. (Moore, "Medical Ophthalmology," J. and A. Churchill, Publisher)

tant." Gunn observes, "ophthalmoscopic examination is one of the most ready clinical means for the early detection of important arterial changes," and Friedenwald notes, "the

most important aspect of ocular and especially retinal arteriosclerosis is its diagnostic value in relation to general vascular disease." Cabot writes, "arteriosclerosis may appear earlier or more clearly in the retina than elsewhere."

The pathologic histology of retinal arteriosclerosis is of interest in interpreting the varied symptomatology. Adams' view is, "microscopically, the process is seen to be due to a chronic inflammatory process, there being a proliferation of the endothelium of the tunica intima, and at the same time new formation of connective tissue and especially of elastic tissue. The endothelial proliferation occurs both in the arteries and veins." The obstruction of the retinal vessels, which those various lesions produce, affects the nutrition of the retinal structures and is therefore a major factor in impaired retinal function.

The arteriosclerotic changes which affect the retina and retinal vessels are many and various. The following abridged outline of deSchweinitz' comprehensive summary presents the usual changes encountered. (Fig. 150.)

"Alterations in the retinal vessels are also caused by chronic nephritis and general arteriosclerosis and present the following ophthalmoscopic appearances: (1) Alterations in the course and caliber of the retinal arteries, such as undue tortuosity, which is not significant unless it is associated with other evidence of disease; in the size and breadth of the retinal arteries, presenting as it were a beaded appearance. (2) Alterations in the reflections from and the translucency of the walls of the retinal arteries, manifesting themselves (*a*) in increased distinctness of the central light streak on the retinal vessel and an unusually light color of the entire breadth of the artery; (*b*) loss of translucency, so that it is impossible to see, as is possible in the normal state, through the artery and underlying vein at the point of crossing; (*c*) positive changes in the arterial walls consisting of whitish stripes, indicating degeneration of the walls or infiltration of the perivascular lymph-sheaths (perivasculitis). (3) Alteration in the course and caliber of the veins, together with signs of

mechanical pressure, manifesting themselves (a) in undue tortuosity, which as in the case of the arteries is not significant except in the presence of other disease; (b) alternate contractions and dilatations; (c) an impeded venous circulation where a diseased artery crosses it. The last is a sign of the utmost importance. (d) Changes in the venous walls, precisely as they occur in the arteries, so that whitish stripes border the vessel and are indications of degeneration in its walls. Often associated with this one may see varicosities. (4) Edema of the retina, manifesting itself (a) as a grayish opacity, which may be present in the immediate neighborhood of the papilla, or in spots over the eyeground and along the course of the vessels, looking like a fine gray haze or in little fluffy islands far out in the periphery. (5) Hemorrhages, manifesting themselves as linear extravasations along the course of the vessels, roundish infiltrations scattered over the fundus, or in droplike form."

He further adds, "the *significance* of these lesions is of serious import. In addition to their relation to nephritis, they may be the forerunners of vascular sclerosis of the brain or indicate the presence of disease of the cerebral arteries. Their subjects are liable to hemorrhage in the brain and all its consequences." The consensus of opinion is that no one sign or symptom in the retinal vessels or retina is pathognomonic of retinal arteriosclerosis. Moore, for example, points out that tortuosity of the arteries of itself is not a reliable index; deSchweinitz emphasizes, however, that a well marked tortuosity affecting the smaller vessels of the macula, indicates a marked degree of arteriosclerosis.

Optic atrophy of gradual development may supervene as a result of the reduced blood supply occasioned by the sclerotic vascular disease. Oatman calls attention to a pulsation in the arteries, so-called "locomotion pulse" as one of the early evidences of retinal arteriosclerosis. He emphasizes as a diagnostic aid the pulsation pressure test, viz.: "Healthy retinal vessels are very compressible while sclerosed vessels are comparatively incompressible. If gradually increased pressure is

applied by the finger to the eye the ophthalmoscope will disclose (1) strong venous pulsation on the disk; (2) arterial pulsation; (3) cessation of circulation and blanching of the vessels. Rigid vessels resist pressure and where retinal arteriosclerosis is advanced neither venous pulsation nor blanching of the vessels can be produced by pressing on the globe with the finger."

Other suggestive symptoms of arteriosclerosis are spontaneous subconjunctival hemorrhages in adults, edema of the lids and recurring conjunctival chemosis. Moore and many other observers stress the diagnostic value of the peculiar phenomena occurring at the arteriovenous crossings, such as indentations and obscuration of the underlying vessel, diver-

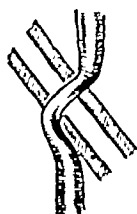


Fig. 151.—To show the riding of a vein over a thickened artery in the retina. The shaded band on each side of the artery indicates its visible coats. From a man of sixty-five whose systolic blood pressure was 265 mm. The appearances were quite unchanged at the end of two years. (Moore, "Medical Ophthalmology," J. and A. Churchill, Publisher.)

sion of its course and interference with its visibility for short distances on either side of the crossing; these changes he regards as evidence of a high degree of sclerosis (Fig. 151). Knapp emphasizes that in appraising the ophthalmoscopic findings, refractive errors, conditions of acute toxemia occurring in acute Bright's disease, severe influenza, and a failing heart must be excluded. Thorington mentions the presence of sclerosis in retinitis pigmentosa. Cerebral arteriosclerosis is not necessarily to be predicated on a retinal arteriosclerosis as the two may not coexist. Herter, however, states that a positive finding of sclerosis of the retinal vessels assumes a similar condition in the cerebral vessels, but not the reverse.

Moore believes that where disease of the retinal arteries is evident, cerebral vascular disease is also present, but that in 30 per cent of cases even an advanced disease of the cerebral vessels may be present without the retinal vessels being demonstrably involved. As to prognosis, Moore states the tenure of life of patients who are the subjects of retinal arteriosclerosis is uncertain, but a considerable number live for several or many years. Adams concludes that the prognosis is dependent upon the associated renal and cardiac changes and that it is aggravated by the presence of albuminuria and that it is better in older people.

**Practical Eye Diagnostic Summary.**—Early manifestations of general arteriosclerosis are frequently seen in retinal vessels. Their early recognition have an important bearing in relation to the cardiovascular-renal group of diseases. The presence of sclerotic changes in the retinal vessels suggests arteriosclerosis, syphilis, or nephritis. Routine examination of the eyegrounds is therefore of outstanding value in general examination.

The important changes to be sought for in ophthalmoscopic examination of the retinal vessels are—undue tortuosity, particularly of the vessels near the macula, beaded appearance—accentuation of the central light stream and sheathings (whitish stripes bordering the vessels) of the sheaths, indentation of and lack of transparency at vessel crossings, locomotion pulse, changes in caliber, retinal infiltrations; in addition, edema (grayish opacity) of the retina, retinal hemorrhages, the pulsation pressure test phenomena, edema of the lids, recurring conjunctival chemosis, and subconjunctival hemorrhages.

### BRAIN ABSCESS

In December, 1930 a young man of twenty-four came under my care suffering from severe, persistent headaches. Several years previously he had had a right simple mastoid operation. Eye examination was negative. Other findings, however, suggested a suspicion of brain abscess, which was concurred in by an eminent neurologist. Blood examination, however, disclosed the Plasmodium malariae of Laverin and the diagnosis of malaria.

This case is cited more particularly to stress the value of "routine" in examination.

The diagnosis of brain abscess is almost always difficult. It is generally accepted that they have their origin as complications of infective processes originating outside the cranial cavity, such as diseases of the ear, mastoid, nasal accessory sinuses, heart, lungs, etc. In making the diagnosis of brain abscess, therefore, it is necessary to establish the causal rela-

tion between the original focus and in addition exclude as possible explanations of the symptoms presented a host of other diseases such as brain tumor, meningitis, apoplexy, cerebral syphilis, encephalitis lethargica, etc. A problem of this magnitude demands that every source of possible aid be utilized. The eye not infrequently exhibits symptoms in brain abscess which may, in connection with the other symptoms, prove of considerable value in the diagnosis and localization. An enumeration of the eye symptoms which may occur in the various types of brain abscess includes the following: Photophobia, diplopia, optic neuritis, papillitis, choked disk, nystagmus, pupillary disturbance, hemianopsia, oculomotor and abducent nerve paralysis and sensory aphasia. The most important of these is optic neuritis. According to Gowers, optic neuritis occurs in two thirds of the cases and if the abscess has existed for more than four weeks it is found in three fourths of the cases; also, that if it is limited to, or more pronounced on one side the abscess is likely to be on that side. Practically all observers agree that the optic neuritis, in particular the swelling of the papilla, is seldom as marked as in brain tumor, and also that optic neuritis and choked disk are more frequent manifestations of brain tumor and meningitis than of brain abscess. It is also said that optic neuritis and choked disk are more common with cerebellar than with cerebral abscess. Choked disk is generally regarded as an expression of extreme increased intracranial pressure, as may occur in brain tumor. It is not a usual manifestation of brain abscess but is more common in brain tumor, occurring in 71 per cent of cases; in brain abscess in 2.2 per cent (Uhthoff), due perhaps to the usual absence of increased intracranial pressure in brain abscess and its usual presence in brain tumor. Sharpe, for example, states, "Unlike most brain tumors (excluding the gliomas) which produce an increase of the intracranial pressure by their added tissue formation or by a blockage of the ventricles, brain abscesses, on the contrary, replace brain tissue so that unless the escape of cerebrospinal fluid from ventricles is blocked by a large subtentorial abscess for-

mation there are produced no signs of a marked increase of the intracranial pressure."

Eggleton's deductions are, "A moderate grade of papilledema is a frequent manifestation of cerebellar abscess; papilledema is frequently seen in occipital lobe abscess; papilledema is usually absent in front lobe abscess; transient or fixed hemianopsia of the homonymous type, for form and colors is a valuable localizing sign of temporosphenoidal lobe abscess and should always be sought for; vertical nystagmus and lateral deviation of the eyes when present are definite indications of cerebellar involvement; ocular paralysis is of no localizing value."

Photophobia may be present in the early stages, but it is of no determining value as to localization or stage of abscess. Diplopia occurs occasionally in temporosphenoidal and frontal lobe abscess. Wyllie states that the state of the pupil does not assist in the diagnosing of the abscess but is of decided value in deciding the stage and the side on which the abscess is located—equal pupils which respond actively to light and accommodation indicate the early purulent stage; if the pupils lose their activity and become sluggish or stable it is an indication of the terminal stage; if unequal, one being widely dilated, the abscess will likely be found on the side of the widely dilated one; if both pupils are widely dilated the abscess is probably large. Vision may be affected and its prognosis is uncertain depending on all the factors entering into the case. While the eye symptoms of brain abscess are of aid in diagnosis their absence is not to be interpreted as an indication that a brain abscess is not present.

**Practical Eye Diagnostic Summary.**—In all suspected cases of brain abscess, a field of vision for both form and color should be taken with especial emphasis on disclosing if an homonymous hemianopsia be present which is a valuable eye symptom, pointing to a temporosphenoidal lobe abscess. The findings on first examination may not be complete but suggestive, later, tests may confirm the early suggestive features, hence, all the foregoing eye tests should be repeated at frequent intervals. The pupils should be carefully examined for equality and reaction. The eyegrounds, especially the papilla, carefully studied for early evidences of optic neuritis.

## BRAIN TUMOR

In June, 1930 a young girl of nineteen was referred to me for an eye examination to determine if glasses might not relieve the severe headaches from which she had suffered for some time. She had recently been operated for gallbladder infection, the diagnosis of this condition being largely based on the presence of gastro-intestinal disturbance, persistent severe headaches and jaundice. No relief resulted from the operation. Eye strain was considered as a possible cause of the headaches. The eye examination disclosed a well-marked choked disk involving both eyes and the diagnosis of brain tumor was made.

The eye symptoms of brain tumor are of outstanding significance, diagnostically and prognostically, and frequently are determining factors in appraising the clinical progress of the cerebral lesion and its proper therapeutic management. It should be recalled, however, that these eye symptoms are not of themselves as a rule determining elements but must be considered only as a part of the clinical ensemble of symptoms presented. The chief eye symptoms of brain tumor are: (1) Those involving the optic papilla and retina; (2) changes in the visual fields for form and color and alterations of the blind spot; (3) impairment of the light sense. Of these symptoms the most important is that affecting the optic nerve head, commonly referred to as choked disk, papilledema, papillitis, optic neuritis or by the German designation, "Stauungspapille." It is present in 80 to 90 per cent of cases. Foster states that choked disk is absent in only 5 to 10 per cent of cases and these are mainly tumors of the frontal brain and of the hypophysis. As a preliminary to the discussion of the symptom, choked disk, it is well to refer briefly to certain anatomical relations of the cranial cavity, brain, optic nerve and retina which have an important bearing on the evolution of this eye symptom and the general accepted theory of its production. (Fig. 152.)

The eyeball, optic nerve and retina are essentially outgrowths of the brain. The retina is in reality an expansion of the brain and the optic nerve may be regarded as a cerebral tract. Each optic nerve trunk is made up of nerve fibers separated by neuroglia and held together by connective tissue.



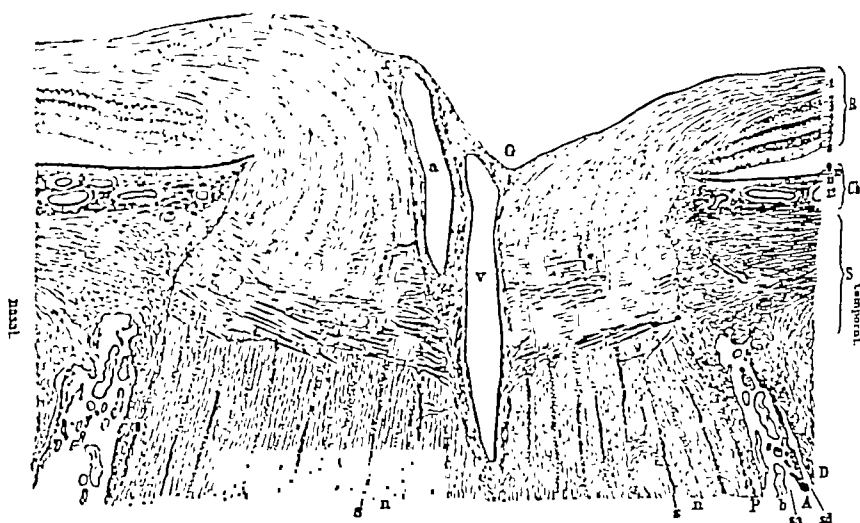


Fig. 152.—Longitudinal section through the head of the optic nerve. In its passage through the scleroticchoroidal canal the optic nerve shows an irregular conical contraction. The fibers of the nerve are collected into bundles, *n*, separated by septa, *s*. Under the form of rows of nuclei, which belong to the neuroglia cells, the continuation of the septa can be followed to the head of the optic nerve. The axis of the nerve is occupied by the central vein, *v*, and the central artery, *a*, which is situated to the nasal side of the vein. The optic nerve is traversed transversely by the lamina cribrosa, which separates the trunk from the head of the nerve. The fibers of the lamina cribrosa arise from the wall of the scleral canal, traverse the nerve in a slightly concave arch (the concavity being directed to the front), and are inserted into the connective tissue that accompanies the central vessels. About at the level of the inner layers of the choroid, the nerve fibers diverge like a sheaf, so as to form a funnel-shaped depression—the vascular funnel, *G*. More fibers pass to the nasal than to the temporal side of the papilla, for which reason the former side is the higher. The fibers of the optic nerve pass over into the fiber layer (1) of the retina. Succeeding this are the other layers of the retina, namely the layer of ganglion cells (2), the inner plexiform layer (3), the layer of inner granules or bipolar cells (4), the outer plexiform layer (5), the layer of the outer granules or of the bodies of the visual cells (6), the limitans externa (7), and the layer of rods and cones (8). The layers of the retina stop short at the head of the optic nerve, the outermost layer, 8, extending the furthest in. The innermost fibers of the sclera which form the wall of the scleral canal, accompany the optic nerve backward and form its pial sheath, *P*, which is in intimate relation with it. At a point further back from the nerve head the outer layers of the sclera are reflected backward and form the dural sheath, *D*, which envelops the nerve loosely. Between these two sheaths lies a third, the arachnoid sheath, *A*, which divides the intervaginal space of the optic nerve into the subdural space, *sd*, and the subarachnoid space,

Lymph channels occur between the connective tissue and the bundles. The nerve trunk is surrounded by three enveloping sheaths; the dura, arachnoid and pia, which are the direct continuation of the cerebral meninges. Between the dura and pia is the intravaginal space which is divided by the arachnoid sheath into the lymph spaces, the subdural and subarachnoid. Both of these lymph spaces originate in and are continuous with the corresponding cerebral channels. These enveloping sheaths terminate by a cul-de-sac in the sclerotic coat of the eye near the lamina cribrosa. The central vessels (artery and vein) of the retina run in the axis of the optic nerve to the optic papilla where they enter the eyeball and spread out over the nerve head as the central retinal vessels. They are presumed to have no anastomosis and are regarded as end-arteries. The connection of the cerebral lymph spaces with the sheaths enveloping the optic nerve, and in particular their termination in a cul-de-sac in the immediate neighborhood of the optic nerve, favors blockade and compression of the nerve at this point. This anatomical arrangement explains the readiness with which an increase of intracranial pressure may by compression affect the nerve head and retinal vessels and produce in the eyegrounds the familiar ophthalmoscopic picture of

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*sa.* Anteriorly, both end by a cul-de-sac in the substance of the sclera; *b*, is the cross section of one of the numerous subarachnoid trabeculae which connect the arachnoid to the pial sheath. In the wall of the scleral canal is seen the cross section of some blood vessels, belonging to Zinn's scleral circle. Between the sclera, *S*, and the retina, *R*, lies the choroid, *Ch*. The innermost layer of the latter, the lamina vitrea, 10, is the one that extends the furthest in toward the nerve head, and the fibers of the nerve are constricted by the edge of the lamina. Upon the lamina vitrea lies the pigment epithelium, 9, which belongs to the retina and which on the nasal side extends as far as the lamina vitrea, but on the temporal side stops somewhat short of it. On both sides the pigment epithelium gets to be thicker and more pigmented toward its edge—a state of things which answers to the choroidal ring that can be seen with the ophthalmoscope. The succeeding layers of the choroid, the choriocapillaris, 11, and the layer of medium and large-sized vessels, 12, do not extend quite up to the optic nerve on the temporal side, because a layer of connective tissue representing a continuation of the sclera juts in between the two. (Fuchs-Duane, "Textbook of Ophthalmology," Courtesy of J. B. Lippincott Co.)

choked disk. The fibers making up the optic nerve along with the vessels imbedded in their substance enter the back part of the eyeball through a rather intricate aperture known as the foramen sclerae and on reaching the interior eye spread out over its posterior inner surface to form a nerve carpet, the retina. The optic nerve trunk does not enter the eyeball at the foramen sclerae through a single large opening but in the following manner (modified from Fuchs). The sclera divides into an outer and inner portion. The outer portion, constituting two thirds of its thickness, is not perforated at all, but is reflected backward and enfolds the trunk of the nerve forming the dural sheath; the inner portion, along with a small portion of choroid process traverses inward forming a septum or diaphragm which is perforated by numerous openings through which the separate bundles of nerve fibers pass. This perforated diaphragm resembles a sieve, hence the name "lamina cribrosa" applied to it. The optic nerve at the foramen sclerae and especially at the lamina cribrosa is tightly enclosed between firm fibrous walls and when swelling of the optic nerve takes place, constriction and strangulation of it usually occurs. Viewed with the ophthalmoscope, the lamina cribrosa, when present, appears on the disk surface as a small stippled zone made up of grayish dots and white interspaces. The dots are the nerve fibers and the white interspaces are the septal partitions between the apertures. The central vessels enter with the nerve fibers, divide and traverse the retinal surface. The separation or diverging of the nerve fibers and vessels on the nerve head produces a funnel-like depression called the vascular or physiologic cup the bottom of which may present a stippled appearance, the lamina cribrosa. The area of entrance of the nerve fibers and vessels to the eyeball is known variously as the nerve head, the optic disk or papilla. The two optic nerve trunks proceed backward from the eyeball and join at the chiasm. In the chiasm the fibers of each trunk divide, semidecussate and form optic tracts, each of which is a composite of nerve fibers from its own and the opposite side, a left and right. The optic tracts

proceed backward respectively to the right and left primary subcortical optic centers and visual areas in the occipital lobe. (Fig. 153.) The nerve fibers of accommodation, convergence and of the pupil pass from the optic tract to the oculomotor nucleus and from this nucleus send fibers in the trunk of the oculomotor nerve to the pupil, to the muscles of accommodation and convergence. This semidecussation of nerve fibers at the chiasm and the distribution of the tracts explains the various pupillary, accommodation, convergence and hemianopic phenomena frequently exhibited in cerebral neoplasms and other intracranial disturbances which often provide important eye symptomatology in the diagnosis and localization of the lesion. The chiasm rests upon the sphenoid bone and is in intimate relation with the pituitary body, the anterior end of the third ventricle, the infundibulum, internal carotids and the meninges.

Many theories have been advanced to explain the development of choked disk, notably the mechanical and the toxic or inflammatory (Fig. 154). The consensus of opinion favors the mechanical theory. Cushing observes, "It seems in all probability a stasis edema from the forcing of the cerebrospinal fluid into the meningeal sheath which invests the optic nerve." Fuchs' comprehensive explanation of the way choked disk may be produced by an intracranial growth is of interest, "A brain tumor as a result of its growth arrogates constantly more and more space to itself within the cranial cavity. Hence, as the skull is unyielding there arises an increase in the intracranial pressure. Owing to this increase the return flow of lymph in and about the optic nerve is impeded and a stasis of lymph occurs producing an edema of the nerve trunk. This edema causes a compression of the central vessels, a compression which makes its influence felt, sooner and to a higher degree, in the central vein of the optic nerve than in the central artery. As there is constantly pouring into the papilla through the artery a quantity of blood which cannot be completely carried away again by the contracted central vein, venous engorgement of the optic nerve and consequently

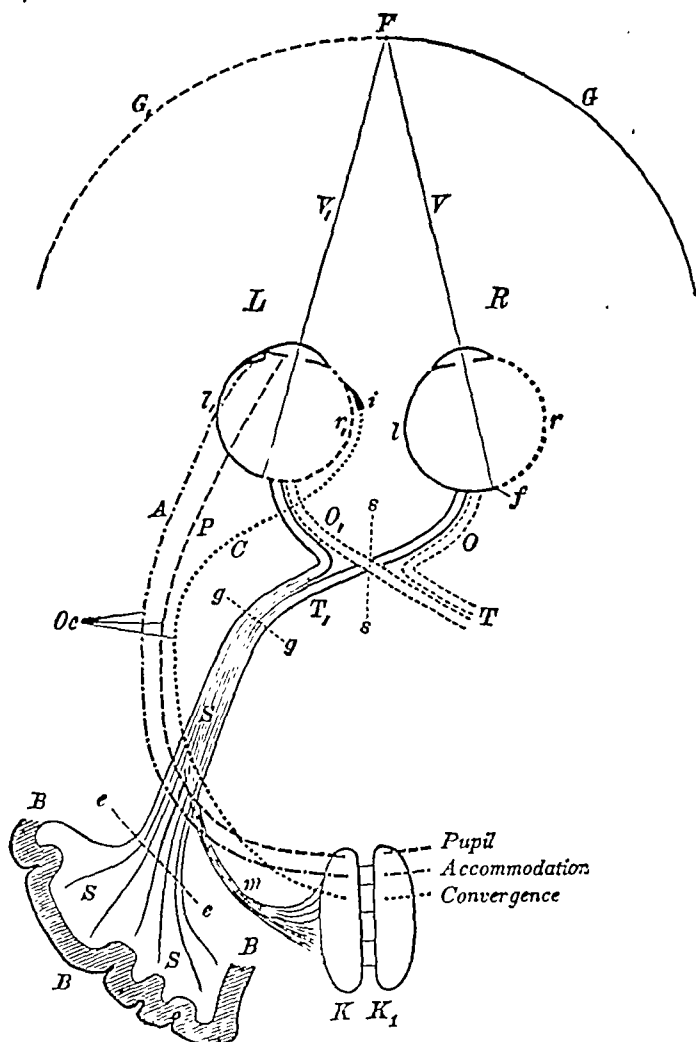


Fig. 153.—Schematic representation of the pathways. The field of vision common to the two eyes is composed of a right half, *G*, and a left half, *G*<sub>1</sub>. The former corresponds to the left halves, *l* and *l*<sub>1</sub>, of the two retinae, the latter to the right halves, *r*, and *r*<sub>1</sub>. The dividing line between the two halves of the retina is formed by the vertical meridian. This passes through the fovea centralis, *f*, in which the visual line (*V*) drawn from the point of fixation, *F*, impinges upon the retina. The optic nerve fibers arising from the right halves, *r*, and *r*<sub>1</sub>, of the two retinae (indicated by the dotted line) all pass into the right optic tract, *T*, while the fibers belonging to the left halves, *l* and *l*<sub>1</sub>, of the two retinae pass into tract *T*<sub>1</sub>. The visual fibers of each optic tract pass to the cortex of the occipital lobe, *B*, forming Gratiolet's optic

swelling of the latter developed. This swelling of the nerve leads to its incarceration at the spot where it fits so tightly

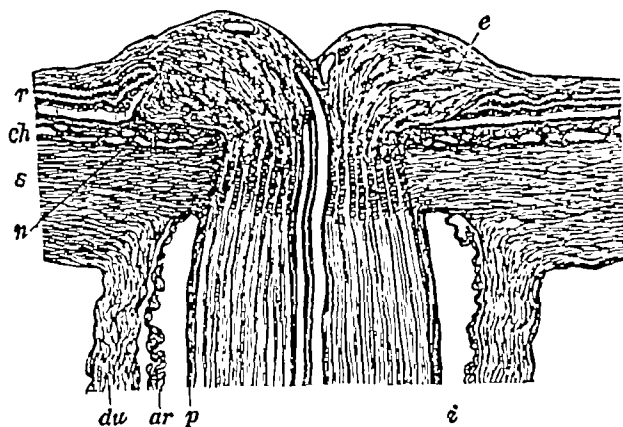


Fig. 154.—Longitudinal section through the head of the optic nerve in choked disk (magnified  $14 \times 2$ ). The disk is greatly swollen, so as to project above the level of the adjacent retina and form at the base an annular protrusion, *n*. There is a cellular infiltration, particularly along the minuter blood vessels, *e*, for which reason the latter appear specially prominent. The retina, *r*, is thrown into folds about the circumference of the disk, in consequence of the swelling of the latter; the choroid, *ch*, and the sclera, *s*, are normal, as is the optic nerve posterior to the lamina cribrosa. Here there is present, simply a dilatation of the intervaginal space, *i*, through accumulation of fluid, by virtue of which the greatly folded arachnoid sheath, *ar*, becomes especially prominent; *du*, dural sheath; *p*, pial sheath. (Fuchs-Duane, "Text-book of Ophthalmology," J. B. Lippincott Co.)

in the foramen sclerae and consequently extreme edema develops in the strangulated nerve head. This edema constitutes what is known as choked disk which therefore consti-

radiation, *S*; the pupillary fibers, *m*, go to both oculomotor nuclei, *K* and *K*<sub>1</sub>. Each of these latter consists of a series of partial nuclei, one of which sends fibers, *P*, to the sphincter iridis, another sends fibers, *A*, to the ciliary muscle (muscle of accommodation), and a third sends fibers, *C*, to the converging muscle (internal rectus), *i*. All three fibers run in the trunk of the oculomotor nerve, *Oc*. Division of the optic tract at *gg* or *ee* produces right hemianopsia, and in the former case there would theoretically be no reaction to light on illuminating the left half of either retina (hemikinesis). Division of the chiasm at *ss* produces temporal hemianopsia. Division of the fibers, *m*, abolishes the reaction of the pupil to light, but leaves the associated reaction of the pupil to accommodation and convergence unaffected. (Fuchs-Duane, "Textbook of Ophthalmology," Courtesy of J. B. Lippincott Co.)

tutes a very important symptom of increase of the cerebral pressure." The ophthalmoscopic picture of choked disk has been summarized by Marcus Gunn in five stages:

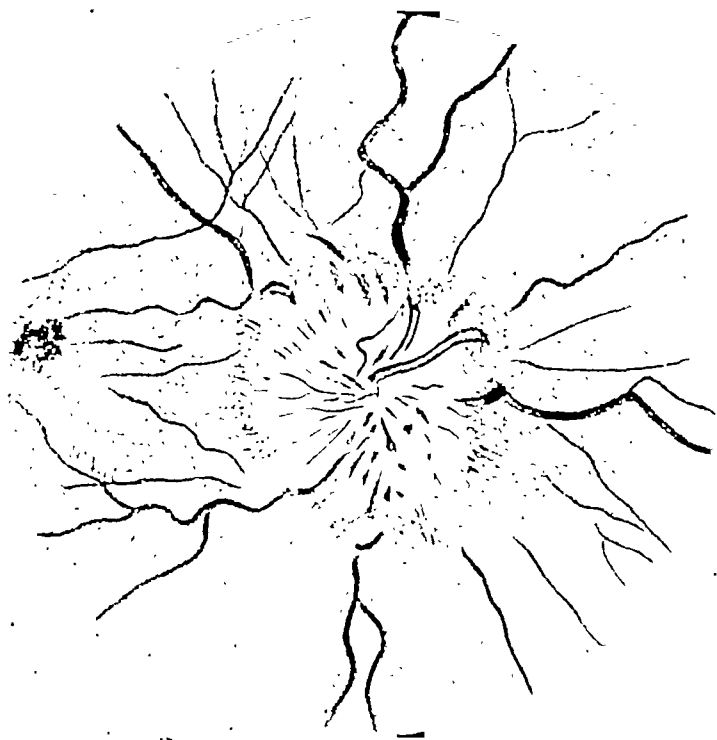


Fig. 154a.—Choked disk at its acme. Scarcely a trace can be seen of the margins of the papilla, but the latter seem to send tonguelike processes into the retina. The papilla is distinctly elevated, as can be seen from the course of the vessels, and exhibits a radiating striation. A number of hemorrhages, also striate in form, give the disk quite a specific appearance. The disproportion between the arteries and the veins is so great at the acme that the former are scarcely visible, while the latter leave the papilla as broad, tortuous bands. Some white patches of degeneration are visible in the retina. There are only a few retinal hemorrhages in this case, but they are often much more numerous. The vision in this patient was normal. (Adam Foster, "Ophthalmoscopic Diagnosis.")

1. The earliest ophthalmoscopic signs are increased redness of the disk, loss of definition in its edges, slight prominence of its surface and narrowing of the physiologic pit.

2. As a rate which varies much in different cases and which seems to bear a decided relation to the degree of intracranial tension, the swelling of the papilla increases, the physiological pit disappears and the disk edges become quite obscured. Along with these signs there is now slight haziness of the surrounding retina and the retinal veins show evidence of retarded circulation.

3. In an advancing case the next alteration consists in further swelling of the papilla so that it becomes more prominent and occupies a larger fundus area, the venous distention becoming more marked. Fine folds not infrequently appear in the edematous retina, particularly between the disk and macula and there may be retinal hemorrhages.

4. The papilla becomes more opaque and sometimes more prominent, the hemorrhages increase in size and number and there are inflammatory exudations on the disk and surrounding retina. At this stage vision has become impaired.

5. The next stage consists in a gradually decreasing vascularity of the papilla, part of its surface becoming paler than normal, while the prominence either persists or slowly subsides. At this time also we first note a change in the branches of the central artery in the form of diminished breadth—the state of atrophy with inevitable blindness.

From the foregoing summary it is evident that in making an ophthalmoscopic inspection of the eyegrounds for suspected choked disk our study of the nerve head should concentrate on the following five cardinal features: (1) Its color and transparency; (2) definition of its margins or disk outline; (3) condition of level; (4) appearance of the physiologic pit; (5) condition of vessels; ratio in size of the retinal arteries and veins; evidences of retinal edema and retinal hemorrhages. The various stage above outlined in an advancing process show step by step progressive involvement of these five cardinal features. The striking eyeground change of brain tumor is that of the nerve head, choked disk. It is markedly swollen and projects into the vitreous. Its edges overhang and the whole appearance resembles a gray mushroom. The vessels



emerging from the vascular funnel ascend over this mushroom swelling and may disappear as they descend its sides. The disk outlines, while more or less disturbed are still defined.

The second striking change is in the retinal vessels, the veins are increased in size and the arteries contracted. The height of the swelling is estimated with the ophthalmoscope by comparing the refraction of the surrounding retina with the summit of the disk elevation, 3 diopters corresponding to 1 mm. of elevation. A generally accepted rule is that the disk swelling must show an elevation of at least 2 diopters in order to be classified as a choked disk. Sharpe deplors the usual custom of relying wholly upon a disk elevation of 2 diopters as an indication of intracranial pressure signifying a brain tumor. He emphasizes that when this amount of swelling occurs in the disk it is a late manifestation of intracranial pressure and of brain tumor and that the patient's chance of operative relief, conservation of vision, etc., correspondingly suffer when reliance is placed on such a late development. He points out that the earlier evidences of disk and retinal vessel involvement which indicate intracranial pressure should be looked for and accepted as definite evidences of increased pressure intracranially. These early signs are slight dilatation of the retinal veins and a blurring of the nasal margin of the disk, no "measurable swelling" of the disk being exhibited. These early disk and vessel changes must be examined frequently to note their progress and they should, he advises, be corroborated as evidences of increased intracranial pressure by lumbar puncture and the spinal mercurial manometer.

Visual impairment is exceedingly variable. It is often normal even in a well marked choked disk. It is not affected early in brain tumor due to the fact that the choked disk in such cases antedates the visual impairment and choked disk is, as a rule, a relatively late manifestation of brain tumor. Impairment of vision, therefore, is not a dependable symptom as a sign that choked disk is not present. It is necessary in every case of suspected brain tumor, even when the vision

is normal, to examine the eyegrounds to determine if a choked disk be present. In brain tumor the disk involvement is almost always sooner or later bilateral. Horsley believes that it is apt to appear earlier on the side of the lesion. Neither the size of the tumor, the age of the process, its situation, its unilateral exhibition or intensity are of dependable diagnostic or localizing value. Small tumors frequently cause choked disk while large ones fail to produce the symptom. Tumors of the posterior fossa (cerebellum) are the ones with which it is most frequently encountered and it is usually an earlier symptom in tumors of this locality than in tumors of the cerebrum. Cerebellar tumors and those in the midbrain and the thalamus are reputed to produce a more intense choked disk with rapid invasion of visual function than those of the cerebrum, the subcortical, parietal or frontal regions. Tumors of the parieto-occipital regions, of the corpora quadrigemina and of the cerebellum are said to produce the highest percentage of choked disk and that pontine tumors and those of subcortical origin comprise the majority of cases in which the symptom is absent. The types of brain tumor usually encountered are glioma and sarcoma, in children the solitary tubercle. Choked disk is not exclusively a symptom of brain tumor; it may be present in albuminuric retinitis, brain injuries, concussion, apoplexy, thrombosis, the internal type of hydrocephalus, meningitis, etc. The visual field changes which may be exhibited are concentric contractions, possibly inversion of the color fields and enlargement of the blind spot. The pupillary symptoms manifested are occasionally of helpful diagnostic value. Radiations of white lines or dots about the macula resembling the "stellate figure" associated with albuminuric retinitis, sometimes occur (in 15 per cent, Patton).

**Practical Eye Diagnostic Summary.**—There are no external changes of the eyeball which suggest a brain tumor. Vision may be normal in a patient with brain tumor even when there is a well marked choked disk present. Choked disk is a dependable symptom of brain tumor, occurring in 80 to 90 per cent of cases. The only safe course in all suspected cases, particularly those which exhibit the familiar symptom triad of headache, vomiting and vertigo,

commonly associated with brain tumor, is to examine the eyegrounds with the ophthalmoscope. Such examinations should be repeated at frequent intervals. Choked disk is a relatively late manifestation of brain tumor. Early eyeground evidences of increased intracranial pressure are slight dilatation of the retinal veins and blurring of the nasal margin of the disk without a measurable swelling of the disk. These should be looked for and confirmed by lumbar puncture and the spinal manometer. The specific ophthalmoscopic evidences of choked disk are a grayish swelling of the disk surface of a mushroom character reaching a height of not less than 2 diopters, the definition of its margins being more or less maintained, the vessels being interrupted or disappearing as they descend along the sides of the disk swelling; the retinal veins being dilated, the arteries contracted. Such changes are, as a rule, bilateral but may be unilateral or more accentuated on one side. Any change, however, of the disk, such as increased redness, blurring of its edges, slight prominence of its surfaces, etc., should cause concern and the possibility of a brain tumor may be considered until it has been definitely excluded. A visual field test for form and color and of the blind spot should be included in the examination.

### EPIDEMIC ENCEPHALITIS

(Encephalitis Lethargica; Sleeping Sickness; Nona)

This disease has an added interest in view of the recent epidemics in Paris, Illinois, in 1932, and in St. Louis city and county in 1933.

All medical writers are in agreement that eye symptoms are almost always a conspicuous feature of this disease, particularly in its early stages, and that their presence in connection with other symptoms is of distinct value in establishing the diagnosis.

Barker, for example, points out that "In the acute or florid stage or first main stage, we meet most often with either, (1) a somnolent-*ophthalmoplegic* syndrome or, (2) an irritative hyperkinetic syndrome (either choreatic or myoclonic)," and he adds that "a triad of symptoms—fever, somnolence and *ophthalmoplegia*—characterize the lethargic type of encephalitis."

Among the eye symptoms which have been observed in this disease are the following: Ptosis, diplopia, accommodative pareses or paralyses, *ophthalmoplegia* of all varieties, complete partial ex- or intrinsic, impairment of globe movement upward or downward, nystagmus, "oculogyric crisis," blepharospasm, inequalities and irregularities of the pupil, im-

paired pupillary reflexes, mydriasis, myosis, Argyll Robertson pupil, optic neuritis, papilledema, oscillation of the globe, photophobia, "myostatic rigidity" of the eyes, etc.

An analysis of these ocular manifestations discloses that practically all of those enumerated have as their underlying pathology a paresis or paralysis of the nerves which supply eye structures and upon which these structures depend for functional integrity.

The pareses or paralyses of the various ocular structures are more or less erratic and capricious in their exhibition, ranging from a paralysis of *all* the eye muscles, so-called *total ophthalmoplegia*; or attacking only all the external muscles of the eye, so-called *external ophthalmoplegia*; or perhaps only the sphincter pupillae and ciliary muscle, so-called *internal ophthalmoplegia*; or only paired ocular muscles, such as the external rectus of one eye and the internal rectus of the other, so-called *associated or conjugate paralysis*. Two outstanding characteristics are usually conspicuous in the eye symptoms of epidemic encephalitis: (1) They are often temporary and evanescent in duration; erratic in course and behavior and exhibit unpredictable and unstable clinical vagaries as to onset, tenure, recurrence or permanency; (2) frequently they also manifest a "selective" tendency; for example, of a group of ocular muscles supplied by the same nerve, only a few "selected" muscles—perhaps only one—of the group will be attacked. Various similar pareses and paralyses also occur in syphilis, tabes, diphtheria, influenza, rheumatism, exposure to cold, various spinal and cerebral lesions, tuberculous meningitis, diabetes, toxic agents, ptomaine poisoning, etc., and these, therefore, must be excluded as etiologic factors. The presence of an Argyll Robertson pupil, for example, may be confusing. This pupillary phenomenon occurs quite regularly in tabes and syphilitic infection. Adler points out that if it be manifested in epidemic encephalitis it disappears rather promptly, while in syphilis it persists.

Pupillary disturbances, such as impaired reactions, inequalities, miosis, mydriasis, etc., occurring in epidemic en-

cephalitis are, as a rule, evanescent, vacillating, frequently disappearing quite promptly and perhaps recurring. In contrast, such phenomena occurring in spinal and other cerebral lesions are more stable, constant and persistent. The motor ocular nerves, notably the third and sixth, less commonly the fourth, usually bear the brunt of the ocular invasion and produce such symptoms as disturbance involving pupillary reaction, its form, size, etc.; accommodative impairment; restriction of ocular and lid excursion; diplopia, ptosis, etc.

It is customary to refer to so-called early and late symptoms. Among the symptoms which are frequently referred to as early ocular manifestations are ophthalmoparesis, which Stevens states occurs in 75 per cent of the cases; the extrinsic muscles of the eye are affected more frequently than the internal. Moore states that of 168 cases reported by the London Government Board, in 20 per cent diplopia was an early manifestation; the symptom disappeared rapidly as the disease evolved. Late ocular symptoms, those associated with the so-called residual or of the postencephalic parkinsonian stage, are blepharospasm, nystagmus, convergence, paralysis, anisocoria, oculogyric crisis, myostatic rigidity of the eyes.

The oculogyric crisis symptom as referred to by Williamson-Noble, "consists of spasmodic attacks of conjugate deviation of the eyes, most frequently vertical and often associated with a marked emotional factor. It is apt to be regarded as a manifestation of hysteria." The myostatic rigidity of the eye symptom, so named by Cords but first referred to by Nonne, is described by Barlow as follows: "The face has a masked-like appearance, the action of the facial muscles appears to be entirely abolished, and there is not a trace of mimicry in the face, the eyes are expressionless and stare vacantly into space or at some fixed object for many minutes and even hours at a time. Stellwag's sign is also present. It is not a question of paralysis of the eye muscle in these cases; when the patient is aroused the eyes can be moved with an effort, but they soon assume the same fixed position." It is generally accepted that optic neuritis, papilledema or fundus

changes are infrequent manifestations. Foster Moore believes that ptosis is the most common symptom; it is usually bilateral.

**Practical Eye Diagnostic Summary.**—An eye investigation should be included in the general examination of suspected cases.

It should be particularly directed to the lid and globe movement, the appearance of the pupil and the pupillary reactions, the accommodative and convergence range and an inspection of the eyegrounds.

### DIABETES

The ocular manifestations of diabetes are many and varied, involving the lens, optic nerve, choked disk, retrobulbar neuritis, retina, choroid, ciliary body, vitreous, external ocular muscles, the accommodation and refraction. The incidence of ocular involvement in the disease is reported as from 20 to 33 per cent (Knapp). Groenouw classifies the eye lesions in order of frequency as follows: Cataract 30 per cent; retinitis 23.5 per cent; optic neuritis 5.7 per cent; ocular muscle disturbance 3.9 per cent. Other manifestations occurring are refractive changes (including accommodation), vitreous opacities, iritis, thrombosis of retinal vein, hemorrhagic glaucoma and optic atrophy. Of these ocular symptoms those most commonly met with in diabetes are *disturbances of vision accommodation and refraction, cataract, retinitis, and retinal hemorrhages*. Hirschberg states that the most common ocular manifestation is a contraction of the range of accommodation. DeSchweinitz believes that premature presbyopia with failure to accommodate is a common and early symptom. Changes in refraction, an increase of hypermetropia or the development of myopia, also occur. Inability to see clearly at the reading distance is common. Disturbances of vision, particularly near vision, and the necessity for frequent changes of glasses is, therefore, suggestive of a diabetic ocular invasion. Visual impairment is of frequent occurrence and in general is said to be more accentuated in diabetes than in albuminuria. The degree of impairment is dependent upon the extent and the distribution of the fundus changes. Fletcher states that "of the ocular complications cataract is the com-

monest." Stevens observes "Cataract usually of the soft variety and bilateral occurs in about 5 per cent of cases; it may be present in diabetics young or old." Two types of cataract occur in diabetes; one in young patients which is characterized by a rapid onset and development, and the other in the old which evolves gradually. Foster remarks that, "when a young person develops in both eyes within a few weeks from no known cause, cataracts which are evenly developed and when complete, may be seen by oblique illumination to be bluish white with sectors radiating from the center that have a luster like that of mother-of-pearl, an examination of his urine will almost certainly reveal that he has diabetes mellitus."

Fuchs' view is that "the prognosis of diabetic cataract, as far as the operation upon it is concerned, is less favorable than in senile cataracts, because in diabetes wounds show less resistance to infection and moreover diabetes predisposes to iritis." Most observers are in agreement with this view and urge that before operation be undertaken the diabetic process should be reduced to the minimum and the patient's physical condition improved to the utmost.

**Diabetic Retinitis.**—Some difficulty may be experienced in properly evaluating the retinal changes due to an arteriosclerotic or albuminuric pathology which may coexist with the diabetes. It is generally regarded that diabetic retinitis is not of frequent occurrence; that it is bilateral; that it affects mostly older subjects and that it is a late manifestation of diabetes. DeSchweinitz mentions that in any case of diabetes of long duration, retinitis is seldom absent although it may sometimes be difficult to find the lesions because they may exist in the periphery of the eyeground and especially so if the complication of high myopia or cataractous lens is present. Moore states that retinitis affects older people only and that it does not occur under the age of thirty-five. Fuchs thus describes the retinal picture: "It is characterized in many cases by the presence of small, brilliantly white spots in the retina which chiefly occupy the region of the macula lutea and

its vicinity, without, however, presenting a stellate arrangement as in albuminuric retinitis. Sometimes by the confluence of small dots one or two large patches are formed which show by their crenated borders that they are composed of smaller dots. Between the white patches lie punctate extravasations of blood. The rest of the retina is transparent and the papilla too is unaltered. In other cases this characteristic picture is not present; in fact, diabetic retinitis may actually appear



Fig 154b.—Diabetic retinitis. Extensive white exudations in the macular region. (deSchweinitz, "Diseases of the Eye.")

under the guise typical of albuminuric retinitis or closely resemble a retinitis circinata. Very rarely in young diabetics, especially when nearing death, *retinal lipemia* is found, *i.e.*, a condition in which on account of fat in the blood the retinal vessels appear reddish-white or pure white." Moore calls attention to some special features which he regards as particularly suggestive of a diabetic retinitis: (a) The patches of retinal exudate in diabetes tend to have sharp cut edges,



are often solid and soapy or waxy looking, are usually distributed in an irregular manner and sometimes form an irregular ring well wide of the macula; (b) a star figure is uncommon and if present it does not acquire the degree of symmetry that may be seen in renal cases; (c) the soft edged cotton wool patches so frequent in severe renal cases do not appear in diabetes; retinal edema is never so marked and thus retinal detachment does not result; (d) retinal hemorrhages are generally in the deeper retinal layers and, therefore, are roughly circular in outline instead of being flame shaped; (e) the circular retinal pigment spots which are not rare in the later stages of retinal retinitis are not seen in diabetes.

Hirschberg describes a retinal picture called central punctate diabetic retinitis which he also regards as characteristic of diabetic retinitis. The optic disk is normal and the retinal vessels are not visibly sclerosed. There is no hyperemia or edematous clouding of the surrounding retina. In the zone adjacent to the optic nerve between the superior and inferior temporal blood vessels groups of punctate, small, discrete, sharply defined white spots are seen. Between the spots numerous small punctate or striated hemorrhages are found. The spots may extend to the nasal side. Thorington observes that "the snow bank about the disk and the macular star, commonly seen in albuminuric retinitis, are absent in diabetes."

**Hemorrhages.**—Hirschberg (quoted by Knapp) divides retinal hemorrhages in diabetes into four groups: (1) Small punctate hemorrhages; (2) larger hemorrhages with vitreous opacities; (3) hemorrhagic infarct of the retina; (4) hemorrhagic glaucoma. It is believed that diabetic subjects are prone to develop intraocular hemorrhages and that a diabetic retinitis exhibits more hemorrhages than the albuminuric retinitis. They are small and since their seat is below the nerve fiber layer their outline is more or less circular and not, as in albuminuric retinitis, flame shaped due to the location of the latter in the nerve fiber retinal layer. Small dotlike retinal hemorrhages point to a diabetic condition. The hemorrhages may be limited or extensive and vitreous opacities may result

from a leakage of blood into the vitreous. Rarely hemorrhagic glaucoma may similarly be set up. Iritis is uncommon. Retrobulbar neuritis may occur with a relative central scotoma. The prognosis for life in a well marked diabetic retinitis is to be regarded as unfavorable though somewhat better than that of an arteriosclerotic or albuminuric retinitis. The visual prognosis likewise is uncertain.

**Practical Eye Diagnostic Summary.**—In all cases of suspected diabetes an examination of the eyegrounds should be made. The fundus changes are small, brilliantly white spots in the macular area and retinal hemorrhages. The picture may resemble an albuminuric retinitis. Usually the retina and disk present no changes. Suggestive symptoms are disturbance of vision, particularly near vision and the necessity for frequent change of glasses. Cataract is a frequent complication. The rapid development of a cataract in both eyes in young subjects is suggestive of the presence of diabetes mellitus.

### NEPHRITIS

In May, 1933 a patient aged forty-five consulted me for reading glasses. His general physical condition he regarded as excellent. He presented no external evidence of ocular difficulty. His vision was practically normal and his only ocular complaint was of slight difficulty in reading the telephone directory. Examination of the eyegrounds disclosed an albuminuric retinitis and on subsequent general examination the diagnosis of Bright's disease was made.

The value of eye symptoms in nephritis is unquestioned. Clinicians generally emphasize their importance in contributing to the diagnosis and more especially in predicting a prognosis. It is a common experience for ophthalmologists to discover first eye pathology, suggestive or perhaps determining nephritis in patients who had regarded themselves as being in good condition. These facts are so well recognized that an examination of a case of nephritis cannot be regarded as complete unless an eye investigation has been included. The list of eye symptoms which have been attributed to nephritis is an extensive one. The most important may be summarized as follows: Noninflammatory edema of the eyelids, usually bilateral and involving, as a rule, the lower lids; spontaneous subconjunctival hemorrhage, especially of the recurring type, occurring in elderly people; chemosis of the conjunctiva; epi-

scleritis; exophthalmos; diplopia; vitreous hemorrhages; albuminuric retinitis; retinal hemorrhages; retinal detachment; hyperemia of papilla; optic neuritis; papillitis; choked disk; optic atrophy; visual field changes; impairment of vision to blindness.

Of these the most important is *albuminuric retinitis* which is said to occur in 33 per cent of cases. It is exhibited most

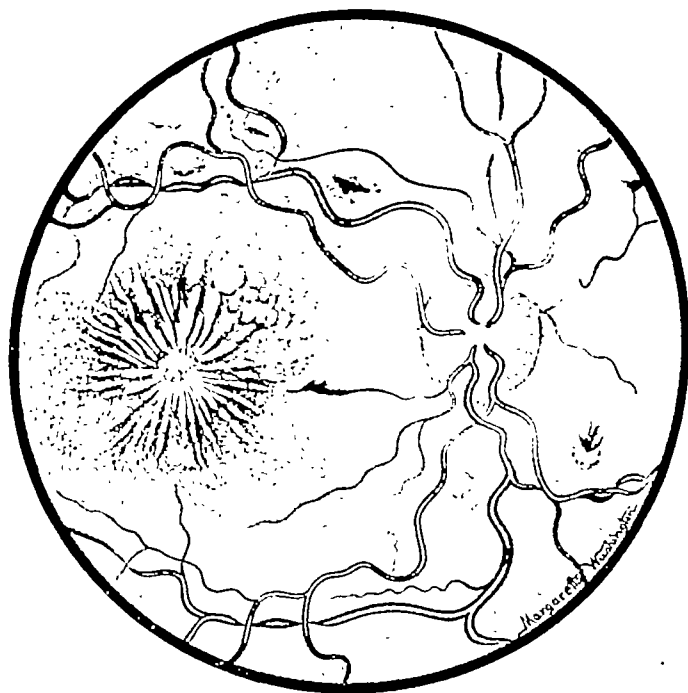


Fig. 154c.—Albuminuric retinitis; star-shaped figure in the macula; the circulation in the distended veins impeded where the latter are crossed by the arteries which are undergoing sclerotic changes. (deSchweinitz, "Diseases of the Eye.")

frequently in the small contracted kidney; next, in the chronic diffuse parenchymatous; next in the acute parenchymatous (scarlatina, etc.) and least in the amyloid degeneration. It involves specially the optic nerve and papilla, the macular region, the retina and the retinal vessels. The outstanding features of albuminuric retinitis of the typical type disclosed by

ophthalmoscopic examination are white spots in the region of the macula; these may take on the aspect of lines radiating from the fovea, but not necessarily invading it. Ultimately as a rule, these spots completely surround the macular region forming the so-called "star figure." The disk is encircled in toto or partially by round white or yellowish-white masses which resemble snow. Hence the name given them of "snow bank"; retinal hemorrhages occur either minute or of greater extent, irregularly distributed and assuming round linear or flame-shaped forms. The retinal vessels may or may not be obscured in areas by these and the vessels often exhibit changes characteristic of arteriosclerosis previously referred to. The retina is swollen, edematous and in areas, as a result, where these changes are marked it is opaque. The optic papilla is commonly involved, varying in degree from hyperemia and neuritis to well marked choked disk. Optic atrophy may eventuate as a sequel. These various changes are associated with two pathologic forms, the *inflammatory* or *exudative*, or the *degenerative*. Either of these types may be exhibited alone or in combination. Depending upon the dominance of the several lesions the appearances, according to Gowers, may be designated as degenerative, hemorrhagic, inflammatory or neuritic. The eye involvement is almost always bilateral. Vision is affected, varying in degree from slight impairment to blindness, depending upon the severity, the stage, the character, location and extent of the fundus lesions. Some degree of permanent impairment of vision is, as a rule, to be anticipated. Retinal detachment may occur and is of serious import from the visual standpoint, the prognosis for reattachment being uncertain. Occurring in the nephritis of pregnancy the prognosis is, however, more favorable. The prognostic value of albuminuric retinitis is of outstanding importance. There is a unanimity of opinion among clinicians that a well marked albuminuric retinitis in association with nephritis portends a tenure of life, in approximately 90 per cent of cases, not exceeding two years. Some reservations as to the interpretation of the eye findings in albuminuric

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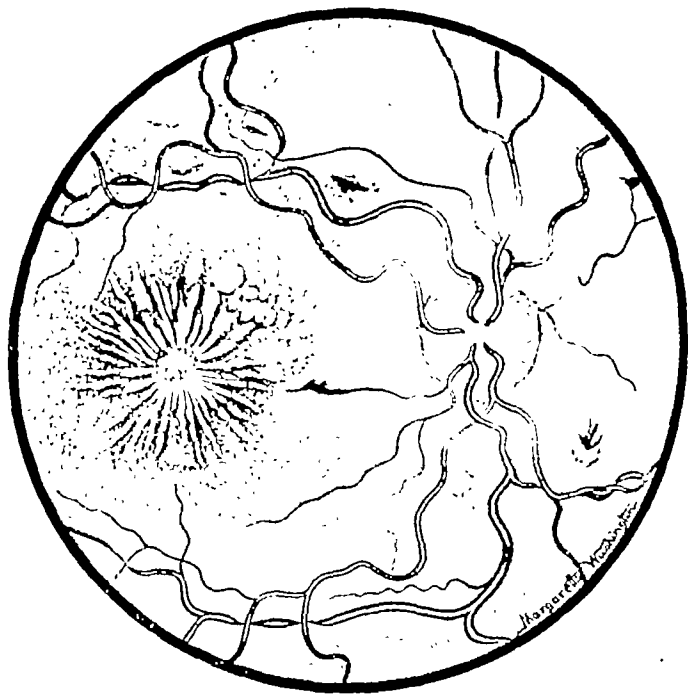


Fig. 154c.—Albuminuric retinitis; star-shaped figure in the macula; the circulation in the distended veins impeded where the latter are crossed by the arteries which are undergoing sclerotic changes. (deSchweinitz, "Diseases of the Eye.")

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retinitis are important to note. The ophthalmoscopic picture, for example, as Foster points out, is not determining in establishing either the variety of renal lesion or the stage of the disease. Neither is the "star figure" exclusively a sign, since it may be found also in retinal arteriosclerosis, diabetes, brain tumor, lead poisoning and acute infectious diseases, in changes affecting the optic nerve, the papilla and in choked disk, pernicious anemia and leukemia.

**Practical Eye Diagnostic Summary.**—An examination of a case of nephritis without an inspection of the eyegrounds is incomplete. The eye findings, both diagnostically and prognostically, are too important to be ignored. The outstanding change to be looked for with the ophthalmoscope is the so-called "albuminuric retinitis," the characteristic changes of which are the star-shaped figure around the macula, the "snow banks" about the disk, retinal hemorrhages, edematous retina and involvement of the disk as an optic neuritis or possibly choked disk.

If time permitted many other general conditions which more or less regularly exhibit eye symptoms might be discussed in detail. Among these are the following:

#### HEAD INJURIES AND SKULL FRACTURES

It is of the greatest importance in these cases to ascertain the state of the intracranial pressure. Such knowledge may safeguard the patient against compression of the medulla and be the deciding factor in operative decision. An increase of intracranial pressure is often manifested by an optic neuritis, choked disk or various pupillary symptoms. In all head injuries and skull fractures, therefore, an examination of the eyegrounds should be made and repeated at frequent intervals.

#### TABES

Eye symptoms are almost a regular accompaniment of tabes and are of definite value in establishing the diagnosis. The chief eye symptoms are Argyll Robertson pupil, which observers estimate occurs in 76 per cent of cases, often as an early symptom; optic atrophy in approximately 20 per cent of cases, also often an early symptom; ocular palsies and alterations in the visual fields, particularly those for color.

## SYPHILIS

All the structures of the eye, with the exception of the lens, may be affected by syphilis in any of its stages. The uveal tract—iris, ciliary body, choroid—are the structures most commonly involved. Both eyes are ultimately affected. A practical clinical observation is that in all eye diseases which prove intractable to treatment the possibility of syphilis being a factor should be excluded.

## PITUITARY BODY

Anatomically, the relation of the pituitary body to the optic chiasm is exceedingly intimate and in consequence eye symptoms are frequent and often a determining manifestation. Changes in the visual fields, producing the various types of hemianopsia, are of special significance. Amblyopia, exophthalmos, pupillary phenomena, and nystagmus are also encountered. In a suspected case of pituitary disease a visual field should always be taken.

From the foregoing brief résumé of the subject, *The Value of Eye Symptoms in the Diagnosis of General Disease*, the following conclusions are warranted:

1. A very considerable number of general diseases exhibit eye symptoms during their clinical evolution and these eye symptoms are frequently of value as an aid to diagnosis and prognosis.
2. An eye investigation should be included as a routine measure in general physical examination. The details of such an examination are relatively neither excessively time consuming nor unduly technical and are definitely within the scope of the general physician.
3. Training in the use of the ophthalmoscope and the details of ophthalmologic examination in the study of general disease should be stressed and routinely applied in undergraduate teaching.





## CLINIC OF DR. MICHAEL HIGGINS EBERT

### COOK COUNTY HOSPITAL

#### RINGWORM OF THE SCALP

Case I.—This boy of six is brought in by his mother because she has noticed "bald spots" in his scalp. The first of these appeared four weeks ago and now is as large as a silver dollar. The later ones are smaller. On questioning her we learned that a younger child in the family also has one or two similar spots. The disorder causes the child no discomfort. On examining the scalp we find that the involved areas are circular, coin sized, and not completely bald (Fig. 155). There are a few stumps and stubs of

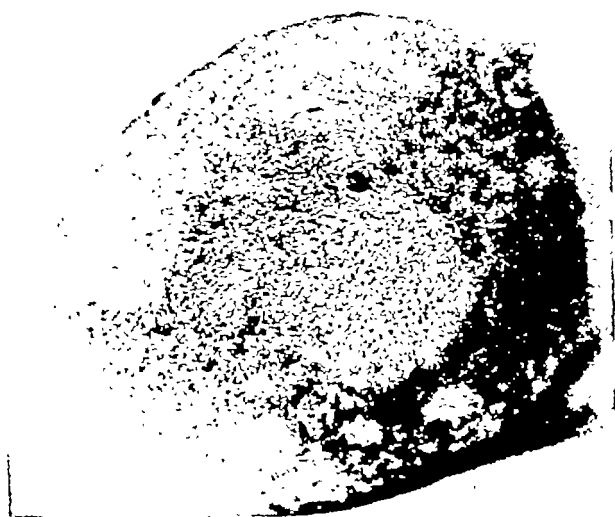


Fig 155.—Ringworm of the scalp due to *Microsporon audouini*.

hair remaining which can easily be epilated. The whole area is covered with a fine grayish scale. Had the mother used some home remedies, the scale might well have been absent. We pull out several hair stumps and place them on a glass slide, cover them with a coverslip and allow a few drops of 15 to 20 per cent potassium hydroxide solution to flow under the slip. The preparation is then set aside to be examined after an hour or two. A similar

preparation is made from the scales which are scraped off the scalp and placed on another slide. The potassium hydroxide solution softens the horny material in the hair and epidermal scales, and clears them so that fungus spores and mycelia become visible.

While the material is softening we will discuss the differential diagnosis of this case. Alopecia areata is not uncommon in children. It produces well defined circular areas of baldness which occur erratically in the scalp. If the scalp has not been treated, the baldness is complete in the affected areas when the lesion is recent. The surface is white, shiny, but not atrophic. If the process is active, short hairs, about  $\frac{1}{4}$  inch long, are found near the active margin which look like exclamation points. These hairs are nearly normal in caliber and color distally, but near the scalp are fine and atrophic. This gives them the appearance of an exclamation point. However, if the bald spot be of some duration, fine, new lanugo hairs may have regrown, giving it a fuzzy appearance. If the scalp has been treated with strong ointments or other preparations, a secondary dermatitis may result in the affected patches, making the diagnosis more difficult. The essential features are still present and there is no history of other members of the family being similarly affected.

Discoid lupus erythematosus may produce round bald patches in the scalp. These are dull red and may or may not be scaly. The follicular openings are dilated, and other similar plaques are usually found present in the ears or on the face of the patient. The patches heal with atrophic scars which result in a permanent loss of hair in the area. Lupus erythematosus in a child of this age would be unusual.

Now let us examine our preparations, first with the lower power of the compound microscope, cutting down the light to a minimum. We find that the proximal portion of the hair root is covered with a sleeve which is made up of a mosaic of thousands of tiny spores set closely together. Under the high dry magnification we find these spores look like little circles. The scales are next examined and are found to contain branching fungus mycelia. This is the characteristic

picture of a microsporon infection. The procedure I have described is not a difficult one. Anyone capable of ordinary work with the microscope can easily demonstrate ringworm fungi. Do not be in a hurry. Do not heat the preparations. Allow plenty of time to elapse before making the final examination. Examine several specimens. One should not make a diagnosis of ringworm of the scalp with its attendant social isolation without the microscopic demonstration of the fungus, any more than he would diagnose tuberculosis without demonstrating the bacillus.

The majority of microsporon causing lesions similar to the ones we have seen today are classified as *Microsporon audouinii*. Dr. Gruby, a Viennese who had migrated to Paris, first described this organism in 1844 and named it in honor of a famous French botanist. Exact species determination can be made only by an experienced mycologist by culture on various artificial media.

Occasionally we see cases of this type due to *microsporon lanosum*. This is a fungus of animal origin (cats, dogs, horses, etc.). It usually sets up a little more inflammatory reaction and is more susceptible to local treatment. This variety may attack the glabrous skin outside the scalp or even the beard region in adults.

Each one of these tiny spores has an extremely resistant membrane. Chemicals kill it with great difficulty. It is carried with the scales in the combings from the scalp. It adheres to the inside of the head dress and to the bed linen. If it finally arrives on another child's head, it germinates, sends out mycelia which penetrate the mouth of the hair follicle, grow around the hair root, penetrate the cuticle and finally produce a new crop of spores. You are all well aware that this is an extremely infectious disease. In institutions like orphan asylums, boarding schools, etc., it spreads like wildfire. It is so contagious that formerly special schools were set aside for its victims. It is a real problem even for the sporadic case, for he must be excluded from school just at an age when formal training is indispensable. It may even flare

up in great epidemics like the one in Basle, Switzerland, after the World War. Fortunately, the disease is self-limiting. Shortly after puberty, due to the action of the endocrine glands, a subtle change takes place in the hair and the sebaceous secretions which oil it, so that they are no longer a fit habitat for the *Microsporon audouini*. Thus, a disease which was extremely difficult to eradicate now disappears spontaneously.

**Treatment.**—Two factors conspire to render the treatment of ringworm of the scalp very difficult. First, the fungus proliferates deep in the hair follicles where it cannot be reached by ordinary measures. Second, the fungus spores are extremely resistant to parasitocides in a strength tolerated by the human skin. They can live long periods in dried material and still remain viable. The first difficulty is overcome by temporary epilation, the second by scrupulous cleanliness, keeping the scalp clipped short or better shaved, and by the use of antiseptics which will prevent germination of the spores.

The most effective agent for temporary epilation is the x-ray. This should not be immediately used in every case, however. Fortunately, practically all the forms of ringworm of the scalp with the exception of *Microsporon audouini* respond to topical applications. If absolute species determination by a competent mycologist is not possible, local treatment should be given a thorough trial.

If local measures are to be attempted, any crusts which are present should be first softened by boric acid wet dressings and olive oil, and then removed. The hair should be clipped very short or shaved and washed thoroughly at least once a day with soap and water. The hair may then be epilated in a zone  $\frac{1}{2}$  inch wide about the affected patches with a tweezers or, better still, with a pencil made of pitch. An ointment is freshly prepared by adding 1 drachm of iodine crystals to 1 ounce of goose grease. This is rubbed well into the affected areas and surrounding zone every night. In the morning an ointment of 3 per cent salicylic acid and 5 per cent ammoniated mercury is applied to the entire scalp. The reac-

tion which occurs is a desirable one for it raises the tissue resistance to the fungus infection. However, we may have to abstain from the use of the iodine ointment when the reaction occurs and possibly use a boric acid wet dressing twice a day. The other milder ointment can usually be continued. As soon as the reaction subsides we resume the iodine ointment.

Whatever local application be used, frequent microscopic examinations of the scales and hair stumps must be made to check on the presence of the fungus. After all signs of fungus infection have been absent on repeated examination, the iodine ointment may be discontinued, but a 5 per cent ammoniated mercury ointment or 5 per cent sulphur ointment should be continued as well as the shaving and washing for two months, and repeated occasionally for short periods several months thereafter.

Darier, of Paris, recommends washing the scalp daily, drying it and then painting the whole scalp with a mixture of tincture of iodine 1 part and alcohol 3 parts, this painting to be continued daily or every other day depending on the amount of reaction.

Parkhurst, of Toledo, suggested a régime which has been found highly successful. He keeps the scalp closely shaven, washes it night and morning with soap and water, preferably tincture of green soap. He applies at night an ointment prepared freshly with 10 per cent fresh saturated alcoholic solution of iodine crystals in goose grease. In the morning he applies a salve made up as follows:

Thymol	2 to 6 per cent
Ammoniated mercury	3 to 6 per cent
Salicylic acid	2 to 4 per cent
In benzoinated lard	

The strength of the active ingredients is gradually increased to the point of tolerance. This ointment is applied to the entire scalp.

During the treatment all the toilet articles should be kept separate and rigorously cleansed. The child should wear a

paper cap inside of his usual headdress and a similar one at night. These should be burned after a single wearing. Until the disease is well under control the child should not play with other children. Where there are several children in a family these should be frequently examined to detect incipient cases. Patience and scrupulous care are the most essential factors in the treatment.

If the infection proves intractable to these measures or if the hygienic environment is such that proper treatment of the patient and prophylaxis of other children is impracticable, arrangement should be made for x-ray epilation. Stimulating preparations should be discontinued for at least a week. The epilation should be done only by a physician who is adequately trained and has had plenty of experience. The amount of x-ray which produces a temporary alopecia is so near the amount which produces a permanent alopecia that one should no more attempt this procedure without special training than he would attempt a thyroidectomy without surgical apprenticeship. When properly performed, the hair begins to fall two weeks after the exposure and begins to regrow about one month later. The scalp should be washed carefully every day with soap and water until the fall is complete. Then it should be bathed daily with a 1:5000 solution of bichloride of mercury in 50 per cent alcohol, and a 5 per cent ammoniated mercury or sulphur ointment used daily for two weeks. Later this may be increased to a 10 per cent ointment. The scalp should be watched carefully for reinfection. The local treatment should be continued for several months.

The internal administration of thallium acetate will produce temporary alopecia of the scalp hair. The therapeutic dose is so close to the toxic dose that we are not warranted, I believe, in recommending this measure to the physician. The toxicity increases with the age of the child. In children near puberty the effective dose is almost always dangerous.

**Case II.**—Our next patient is a boy of nine, who presents what appears to be a large flat carbuncle on the scalp (Fig. 156). This has been present for three weeks and is tender and somewhat painful. The lesion is well defined,

the size of a silver dollar, raised well above the surface of the scalp. Its surface is dull red in color, knobby, and feels boggy. Through numerous openings a gelatinous material exudes. A few stumps of hair remain in the surface of the lesion but can easily be epilated. At first glance it will appear that if this lesion were laid wide open with a scalpel it would quickly drain and heal. However, appearances in this instance are very deceptive. This boggy mass is due to another type of ringworm infection, a trichophyton. The particular variety is of animal origin (ectothrix). Most ringworm infections of animal origin set up a considerable reaction in the affected skin. This reaction eventually kills the fungus so it is much harder to find the organism than it was in the first case where the *Microsporon audouini* has learned to



Fig. 156.—Kerion of the scalp.

live almost in symbiosis with the body cells, producing a minimum of reaction and persisting a maximum of time. If we examine several of the stumps of hairs we may find a branching mycelium in the hair shafts.

Treatment should consist of hot wet dressings of boric acid or magnesium sulphate. Follicular pustules may have to be opened to promote drainage. The area should be painted daily with tincture of iodine 1 part, 50 per cent alcohol 3 parts. A preliminary epilation of the surrounding hair is advisable as in *microsporon* infections.



Nonspecific protein injections in the form of typhoid vaccine may be used in addition to raise the patient's resistance.

A type of ringworm of the scalp rarely seen in Chicago but prominent in England and on the continent is the "black dot" or disseminated ringworm infection. It is easily missed unless the scalp is carefully examined for the lesions are small, inconspicuous and widely disseminated. They consist of scaling macules about a single hair follicle or a group of very few follicles. The affected hairs persist as stumps among their healthy neighbors. These stumps may turn on themselves, like a compressed corkscrew, beneath the scales or in the mouth of the follicle. Their appearance gives rise to the term "black dot." The majority of these cases is also due to a trichophyton but of the endothrix variety which is of human origin. Careful search of the stumps of hairs in a potassium hydroxide preparation will reveal the spores which are a little larger than those of *Microsporon audouini* and are enclosed within the hair shaft, are quadrangular in shape and arranged in lines. All cases of localized dandruff should be suspected, especially if any of the hairs are broken off, and a careful microscopic examination made for the fungus.

Ringworm of the scalp may occasionally produce a generalized eruption of a toxic character which is termed an "id" eruption. When the original site of the infection is irritated or inflamed by treatment or secondary infection, some of the spores or perhaps their toxic products get into the general circulation and are carried to the peripheral cutaneous vessels. The skin has become during the course of the disease allergic to the products of the fungus and now reacts with an acute transitory inflammation which destroys any spores that may be present. So search for them is usually fruitless.

In kerion of the scalp a trichophytid is not uncommon. It is follicular, may be lichenoid, papular or consist of scaly patches. It is symmetrically disseminated on the trunk and lasts only a few days or a few weeks or may recur. It may easily resemble measles or scarlet fever. Microsporids are less frequent in occurrence.

The types of ringworm we have discussed, except kerion, heal without scarring. There is another fungus infection of the scalp, fortunately seldom seen in this country, which lasts a lifetime, gradually destroys the hair follicles, leaving an irregular atrophic scar beset with a few remaining wisps of hair. This is favus, caused by *Achorion schoenleinii* (Fig. 157). When well developed and untreated it produces small sulphur-yellow cups at the base of the involved hairs, giving off an unpleasant odor. It may involve the glabrous skin and the nails. The patients that we see here, however, usually come in with irregular areas of permanent baldness. It is

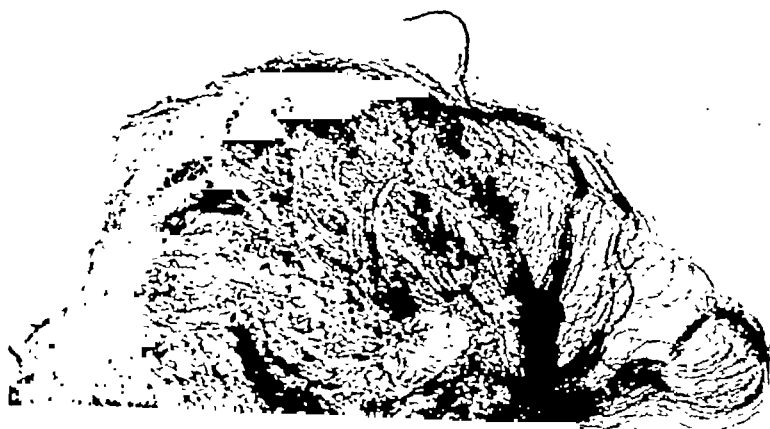


Fig. 157.—Favus of the scalp.

only by careful search of the scales taken from the margin of the atrophic areas that the fungus can be demonstrated. Favus is fairly common in southern and eastern Europe. Immigration officials have attempted to prevent its entrance into the United States. Nearly all the cases we see are immigrants with an occasional native-born patient from an infected family. The disease is contagious and intractable to treatment.

Since the patent-medicine vendors have coined the priceless term "athlete's foot," and made America ringworm conscious via the radio, we constantly hear people say that they have athlete's foot of the hands or athlete's foot of the crotch.

Let us not commit the absurdity of "athlete's foot of the scalp." The fungus which affects the foot can never be transferred to the scalp. So you can reassure unnecessarily disturbed parents who may confuse the terms and fear that they have infected innocent offspring with an organism originally picked up at a Turkish bath or golf club.

## CLINIC OF DR. SIDNEY A. PORTIS

### COOK COUNTY HOSPITAL

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#### GASTRO-INTESTINAL MANIFESTATIONS OF SYSTEMIC DISEASE AND THEIR DIFFERENTIAL DIAGNOSIS\*

THIS morning I would like to bring to you a group of cases that illustrate very clearly how one frequently might overlook some systemic disturbance because the patient complains of symptoms referable to the gastro-intestinal tract. I think I have sufficiently emphasized to you in past lectures the more or less pathognomonic features and symptom complexes related to pathology *per se* in the abdomen. With this background it might be well for us to see what other disturbances could give these same symptoms and yet an exhaustive gastro-intestinal examination give us little or no findings. I am sure you will agree with me that you cannot know gastro-enterology until you have learned general medicine. There are so many conditions outside of the abdomen that simulate intra-abdominal disease that it is only the exceedingly myopic physician who sees only in the light of intra-abdominal manifestations. Many patients are needlessly operated. Many patients are wrecked for their future life because some overzealous physician has neglected to make a very painstaking and very thorough investigation of the patient as a whole. This not only includes a very careful detailed history with a searching physical examination, but also a very exhaustive laboratory and x-ray study. Before one can conclude that the pathology is in the gastro-intestinal tract and that it alone accounts for the symptoms, you must exclude beyond all rea-

\* Clinic given for students of Loyola University Medical School.

sonable doubt any extra-abdominal disturbance which might cause the patient distress.

The first patient of this group of cases which I would like to present is a woman, forty-seven years of age, who consulted me on August 2, 1927 with a history in which her main complaints were belching, and a bitter taste in her mouth. The story is that she had a cholecystectomy and appendectomy nine months previously for the same complaints. No stones were found. For a short time following surgical intervention she was temporarily relieved, however, the same symptoms soon returned. She experienced fulness and distention particularly in the right upper quadrant, coming on at any time and lasting for a half hour, then disappearing spontaneously. She belches considerably and has noted a peculiar taste, not quite bitter, which as a rule comes on within a short time after meals. The distress is never present at night and disappears while resting. She complains of some aching across the back. Her appetite was normal. Her bowels were slightly constipated and she had occasional frequency of urination. The family history was of no importance. She had one pregnancy and no miscarriages. Menstrual history was regular up to the menopause at forty-four. Tonsils and adenoids had been removed at the age of forty, and the cholecystectomy and appendectomy done when she was forty-six.

Physical examination revealed a moderate enlargement of the thyroid gland. There was a coarse tremor of the hands and tongue. Reflexes were intact. Lungs were negative as was the heart. Blood pressure measured 102 systolic and 74 diastolic. There was some tenderness over the right rectus scar through which the gallbladder and appendix had been removed. There was some tenderness over the sigmoid region. The abdomen otherwise was essentially negative. Bimanual examination revealed moderate relaxation of the perineum, uterus anteфлекed and slightly enlarged, and some thickening in the region of the appendages.

Laboratory work revealed the urine containing an occasional pus cell but otherwise essentially negative. The stool showed some undigested food, a little mucus but otherwise was negative. There was no evidence of amebae or cysts. The stomach acidity was 10 free and total 30, with no evidence of obstruction. In the Ewald meal free acid was 35, total 45. Hemoglobin was 93, red count 5,000,000, and leukocytes 8200, with a normal differential count. Wassermann and Kahn tests were negative. The basal metabolism rate was — 14.

Fluoroscopic examination of the chest and abdomen revealed the lungs essentially negative as were the heart and aorta. The stomach was normal and the duodenal bulb filled out normally. The stomach emptied in four hours. Subsequent observations on the bowel revealed normal passage through the colon of the barium given by mouth.

In this particular patient with her gastro-intestinal manifestations, with subsequent surgery for them without improve-

ment, a very exhaustive and intensive study failed to reveal any definite cause for her disturbance. One might be prone in this case to think that her symptoms were entirely functional. However, clinically the patient did not impress me as one who would be predisposed to functional disturbance. She seemed like an exceedingly stable individual. There was one curious fact that might have been overlooked in her clinical story and which was reemphasized on going over the picture with her. That was that when she had a desire to urinate it must be satisfied within a relatively short time. She did not emphasize or mention it in her first visit when her history was taken, but in her story she alluded to a urinary disturbance which was not of much importance to her. Following this line of thought, it suggested itself that the patient might be cystoscoped to see whether any pathology might be found in the urinary tract to explain the symptoms. Interesting as it may be, examination of the urethra revealed a firm, fibrous stricture 2.5 cm. long at the outlet. This was followed by a No. 24 F. Cystoscopic examination revealed a markedly trabeculated bladder, especially on the floor and posterior wall. Both ureteral orifices were normal and there was a moderate trigonal cystitis.

Curious as these findings may be, they are important as far as the patient it concerned because had they been recognized some time ago, useless surgery would have been prevented. Following adequate dilatation at repeated intervals, the patient's gastro-intestinal manifestations entirely disappeared. Her whole outlook on life was very much improved. She is now able to go about, doing her normal daily work, and has entirely forgotten that she has been ill. Yet, had not this patient's urinary tract been very carefully investigated she would have continued to go on from doctor to doctor, probably had more surgical intervention, and been no better off in the end. We were not justified in telling this particular patient that her urinary tract was cause of her symptoms until we had ruled out other causes in the intestinal tract which might account for her symptom complex. In a few

moments I will discuss with you why patients with genito-urinary disturbances give gastro-intestinal manifestations.

The next patient I would like to present is a young married woman of twenty-seven who consulted me on August 20, 1923, complaining of pain in the right side, nausea, lumbar pain, headaches, loss of weight, and a tendency to perspire easily. For the past five years she had pain in the right side which was more or less constant. Appendectomy four years previously for this complaint failed to relieve her symptoms. The pain radiated up into the back and to the right scapula. She felt nauseated when the pain was at its height. It was never referred to the pubic region and she never required opiates for relief. There was some belching and distention after meals.

The noteworthy physical findings were a systolic murmur at the base of the heart, a blood pressure of 142 systolic and 90 diastolic. There was some tenderness over the gallbladder region, and a mobile right kidney was observed. Subsequent gastro-intestinal roentgenograms revealed a prepyloric spasm on the lesser curvature of the stomach which was distinctly tender. Otherwise, the gastro-intestinal examination was essentially negative.

She was treated for a period of three years off and on under gastro-intestinal management, with improvement and relapses. At this time, with the advent of cholecystography the gallbladder was investigated and it was thought to be pathologic. However, her symptoms in general overshadowed the findings in the abdomen. It was thought wise to investigate the urinary tract, because of this mobile right kidney. So, in 1928 Dr. Herman L. Kretschmer reported the following:

"Cystoscopic examination was negative except for a freely movable right kidney. The pyclogram showed the right kidney pelvis in normal position with the patient lying flat on the table, and a prolapse of the pelvis down to the crest of the ilium with the patient sitting up. The kidney could be easily displaced, so that the pelvis could be seen over the spine."

After much discussion and with some reluctance on the part of the urologist it was decided to do a right nephropexy. This was subsequently done and for the last seven years the patient has been completely relieved of all her symptoms and has had no recurrence at all of her gastro-intestinal manifestations.

Another similar case to this only in a male, was that of a patient, aged forty-seven, who consulted me in 1929 complaining of abdominal distress, belching and distention. For the past year or more the patient had had regular, recurring periods of abdominal distress coming on about an hour after meals, especially after the intake of fried and greasy foods, associated with fulness, distention and excessive belching. The past history other than a herniotomy fourteen years before and an appendectomy eleven years before was essentially negative.

Physical examination revealed no noteworthy manifestations. Examination of the urine and stool was negative. The gastric content was normal. Roentgenological examination of the gastro-intestinal tract revealed normal stomach and duodenum. Cholecystogram revealed what appeared to be a

pathologic gallbladder. Subsequent gastro-intestinal management made little improvement in the patient's complaints.

During the course of observation a symptom of frequent and severe distress of the urinary tract developed. Cystoscopic examination was thought advisable. At this time there was revealed a residual bladder urine of 3 ounces and normal bladder tolerance. There were slight, coarse trabeculations on the posterior wall of the bladder, normal ureteral orifices, a depressed trigone with median lobe enlargement, which was definitely elevated and hypertrophied, but with lateral lobes within the limits of normal.

Following transurethral resection of the prostate the gastro-intestinal symptoms have completely disappeared.

Is it any wonder then that gastro-enterologists might become urologically minded occasionally and search at times in the urinary tract for a possible explanation of the gastro-intestinal manifestations? I do not want to leave you with the feeling that this may be a panacea for all gastro-intestinal disturbances, but there is a certain group of these patients which often will continue to be overlooked unless this possibility is sufficiently brought home to them either through their personal experience or by listening to the advice of those who have had trials and tribulations in cases of this sort.

Why should urological diseases give gastro-intestinal manifestations? E. C. Smith in an article some time ago very carefully showed that there was a very definite interrelation of the nerve supply of the upper urinary tract with the organs of digestion. He maintained that since both are supplied by the vagus and sympathetic nerves, any disturbance of the kidney may be reflected through the gastro-intestinal tract. The connecting link is through the celiac ganglion. Therefore, it is reasonable to suppose that impulses originating in the urinary tract can produce gastro-intestinal symptoms without pathologic changes.

The next patient I would like to present is a young lady, twenty-seven years of age, who came in because of pains in the lower abdomen, "dyspepsia," and frequency of urination. Since 1933 the patient has complained of marked frequency and urgency of urination, sometimes urinating as much as six to eight times at night. There was no evidence of any hematuria or pyuria. During this time she has complained of indigestion, consisting of heaviness and a feeling of distention in the epigastrium occurring about fifteen minutes after meals, occasionally relieved by alkalis, associated with much belching.



and heart burn, particularly after greasy foods. She had been somewhat constipated. There had been occasional nausea but no vomiting, and no hematemesis. She gained in weight. She is very irritable, has crying spells, some vertigo and faints frequently.

Physical examination other than slight tenderness over the region of the gallbladder and appendix is essentially negative. The other noteworthy findings are the absence of a corneal and pharyngeal reflex. Bimanual examination was negative.

The urine and stool were essentially negative. Stomach acids were 68 free and 80 total; with Ewald meal 90 free and 100 total. There was no evidence of retention. The blood showed evidence of a secondary anemia with a normal differential. The Wassermann and Kahn were negative. The basal metabolic rate was - 6.

Fluoroscopy of her chest revealed no unusual findings. Stomach was prolapsed into the pelvis for a distance of 2 inches, but was otherwise negative. The duodenum showed a spasm on the greater curvature side at its middle. The second portion showed evidence of stasis and surging. It was curled upon itself and had an S-shaped arrangement. The stomach emptied at the end of four hours.

Subsequent observations at twenty-four and forty-eight hours revealed a definitely tender cecum. The appendix was not visualized and the bowel was moderately spastic.

Cholecystogram showed a normal gallbladder as far as function was concerned.

Chest stereograms revealed no unusual pathology.

Urological examination revealed external genitalia negative, the urethra slightly narrowed, and to quote the urologist her history is entirely inconsistent with the clinical findings. "I do not believe the slight stricture of the urethra which she has is the cause of her frequent urination." To amplify this latter statement, dilatation of the urethra failed to reveal any of the symptoms.

On suitable gastro-intestinal management and with corset and pad to hold up the stomach, no improvement was noted. Following this a course of hospitalization was advised, with elevation of the foot of the bed and the usual measures adopted for the treatment of visceroptotic individual.

Still there was no improvement. The pains in the abdomen were very migratory. It was then decided that possibly there might be some other cause or group of causes which might be accountable for her symptoms, but could not be demonstrated on the basis of organic findings. It is interesting to note that the girl was married at the age of nineteen, was married for three years and then separated for five years. She had three pregnancies, two interrupted and one child living and well. These periods of distress seemed to be definitely related to her sexual habits. Realizing that this might be a basis for her symptom complex, an analytic study was made. It is interesting to note that much of her gastro-intestinal symptoms are closely associated with her inhibited sexual desires. Under the guidance of a very competent analyst, the patient has made steady and definite improvement and much of her gastro-intestinal symptoms have entirely disappeared.

This particular type of a patient is one who usually shows a battle-scarred abdomen and is frequently opened up for surgical intervention at the least provocation. I call it to your attention this morning because there is altogether too large a group of these patients who are going around from physician to physician and from surgeon to surgeon in an attempt to cure their gastro-intestinal complaints, when a careful, painstaking analysis of their symptom complex with the associated findings might lead one to believe that there is a so-called functional basis for their complaints. However, you are not justified in concluding that the functional basis alone is a causative factor until you have made an exhaustive laboratory and x-ray study to rule out the presence or absence of organic pathology.

The next patient is a married woman, forty years of age, who came in because of a bowel distress. For several years she has noticed a tendency to loose stools. She has been told that she has colitis. She knows that if she avoids certain foods she is better. She has lost about 4 pounds in the last few months. She has also noticed some bleeding hemorrhoids. Her past history was that she had one brother and one sister die of pulmonary tuberculosis. She has had two children in the eleven years of married life, both living and well. She has had the usual childhood diseases. About a year and a half ago had a so-called "influenza" with some hemoptysis, and yet complains of no symptoms referable to her chest at the present time.

Physical examination showed some dullness on the right side of her chest, especially in the middle portion. There were numerous moist râles, "clicks." The heart was essentially negative. The liver was not palpable but the spleen extended 1 inch below the costal margin, not tender. There was some tenderness along the course of the colon. Bimanual examination showed no unusual findings. Rectal examination showed large external and internal hemorrhoids. The urine showed no noteworthy findings. The stool was essentially negative except that acid-fast bacilli were found. The stomach tests were within range of normal. Blood showed a secondary anemia of mild grade. Wassermann and Kahn were negative. Basal metabolism was - 1 per cent. Her agglutination tests for bacillary dysentery organisms were negative as were the complement fixation tests for amebiasis. The sputum showed numerous acid-fast bacilli.

Stereograms of her chest revealed evidence of involvement of the right upper and middle lobes. No evidence of cavitation could be seen. Fluoroscopic examination of her stomach and duodenum was negative.

In this particular case the patient was complaining of evidence of a so-called "colitis" for several years, but more in the

last year. She had not lost any weight. There were no chest symptoms, yet one would be willing to believe that her gastro-intestinal symptoms were entirely related to her pulmonary tuberculosis. And since she has been under management at the sanatorium the more or less subacute manifestations of a tuberculous infection are subsiding, her gastro-intestinal symptoms are improving. No attention at all is paid to diet or to foods that formerly disturbed her so far as her so-called "colitis" is concerned.

Many patients with incipient, subacute, or even active tuberculosis show symptoms referable to the gastro-intestinal tract and it is only with a painstaking examination that these facts are brought to light, and in many cases pulmonary findings of this type are accountable for gastro-intestinal disturbance. When the pulmonary pathology becomes quiescent, symptoms referable to the abdomen entirely disappear.

Closely allied with this group of cases and very frequently mistaken in their diagnosis are a group of patients who have disturbances of the thyroid gland. Very frequently patients with symptoms of so-called "masked hyperthyroidism" present a gastro-intestinal picture which is so bizarre in nature and so prominent that the thyrotoxicosis is entirely in the background. This group of cases forms one of the very common sources of error in diagnosis of patients who consult me from time to time. Curious as it may be, it has not only been confined to young individuals but also is seen in elderly patients. Hyperirritability of the gastro-intestinal tract associated at times with hypermotility is a frequent cardinal symptom of this condition.

For instance, as we glance over the next patient, who is a married woman, fifty years of age, who comes in because of pain in the epigastrium and who states that for the last eleven years she has had dull pains in the epigastrium which had no relation to foods. She vomits frequently five to ten minutes after meals, which only slightly relieves her distress. Five and one-half years previously a cholecystectomy was performed for the same symptoms, with only transient relief. She has a great deal of nausea and some belching. Food taking only partially relieves her distress. There is no particular seasonal variation to her discomfort. Three years ago she had an appendectomy, but this gave her no relief. She has been gradually losing weight.

In her past history she had her menopause at thirty-nine. She had six pregnancies, three children living and well. She occasionally got up at night to urinate. Her appetite was poor, due to distress when eating, and there was some tendency to constipation.

Physical examination revealed a moderately obese woman. Thyroid was just barely palpable. The eye muscles only showed a slight weakness. There was a coarse tremor of hands and tongue. The reflexes were intact. The lungs were essentially negative. A systolic murmur was heard over base of heart. Blood pressure measures 150/70.

The abdomen showed numerous scars. There was a large hernia where the appendix had been removed.

Examination of urine and stool revealed nothing unusual. Her stomach acids were absent and 10 free in motor meal, with no evidence of retention, and 20 free and 25 total in the Ewald meal.

Fluoroscopic of her chest and abdomen revealed a large shadow in the substernal region resembling a thyroid. The lungs were essentially negative. The heart was slightly enlarged in the transverse diameter. The stomach was negative. The duodenal bulb filled out normally.

Her Wassermann test was negative and her blood showed a slight secondary anemia. Her basal metabolism was + 62 per cent.

In this particular case no mention was made at all of nervousness, irritability and palpitation and all the symptoms that usually go along with ordinary thyrotoxicosis, and yet over a period of years this lady has had a low grade thyroid disturbance, with gastro-intestinal manifestation, subsequent surgical interference with no relief. We find on repeated metabolism tests the this is an out and out case of thyrotoxicosis.

Particularly interesting is it that she has a substernal thyroid. Following a subtotal thyroidectomy the patient was completely relieved of her gastro-intestinal symptoms, and for the last three or four years has been very comfortable.

If we look at the opposite picture it brings to mind a patient, who is seventy-eight years of age, who was complaining of gastro-intestinal symptoms, accompanied by pain, discomfort and obstinate constipation. She gives a history of the last fifty to sixty years of persistently taking cathartics with only partial relief. Very exhaustive examinations in the past had yielded no results. She was told by a doctor that she had a carcinoma of the stomach. However, one observation of this patient, a very fat, myxedematous type of individual who had apparently lost no weight, would immediately give you the inference that possibly she was over a period of years a hypothyroid individual. Exhaustive examination of her gastro-intestinal tract revealed no evidence of malignancy, and no cause for her long-standing constipation. Her

basal metabolism was — 25, and nothing more was done for this patient than to put her on small doses of thyroid three times a day. No particular attention was paid to diet. The patient is now eighty-three years of age, still continues to take her small doses of thyroid extract and has a daily bowel movement.

Oh, how frequently are patients treated for years and years for constipation, if the clinician would only be alert to know that hyperthyroidism is a very common etiologic factor in producing the so-called "picture of constipation." You are not to believe that hypothyroidism is particularly confined to only obese individuals. It is frequently found in individuals who have normal weight or even weight below their standards. Both these disturbances of the thyroid gland give gastro-intestinal manifestations and yet as far as organic pathology of the gastro-intestinal tract is concerned, it is entirely lacking.

Just the other day, there entered my ward service a patient, some fifty years of age, who had lost some weight and who had been treated for a period of months for gallbladder disease because he had associated nausea, vomiting, some belching, and some fulness after meals. The one symptom which the clinician did not pay enough attention to was that this patient had persistent headache, and furthermore associated with these headaches he had a slight auditory disturbance on the right side. While I am perfectly willing to admit that headaches may be a common symptom of gastro-intestinal disease, I would like to emphasize that the persistence of headaches after the presumed gastro-intestinal disturbance has been under control, should lead you to suspect the possibility of some other cause for the headaches. Two outstanding conditions come to mind, one the possibility of a cerebral neoplasm and the other, a so-called "indurative headache" associated with a hypertrophic osteo-arthritis of the cervical spine. In this particular patient subsequent neurological examination and ventriculograms revealed that the patient had a neoplasm at the cerebellopontile angle. The patient died before operative interference could be done. Necropsy examination revealed a tumor at the cerebellopontile angle.

This is not an uncommon source of error in gastro-intestinal diagnosis and it only goes to reemphasize to you the need of careful observations in each patient as to the cause of their particular complaints.

And how often is the clinician taken off his guard by such a patient as follows:

A young woman, twenty-five years of age, who complained of headaches, nausea and constipation. Patient said she first began to notice constipation ten months ago during pregnancy. Constipation continued through the period of gestation and was later relieved. She states that she had headaches which involved the entire head and were much more constantly present in exacerbations and remissions. These sometimes keep her awake at night, and they are so severe that she sometimes becomes nauseated and faints, and has blurred vision and black spots before her eyes. Of late, she has been more or less persistently nauseated. Nausea has no relation to meals or types of foods. It lasts for about two hours and then disappears. She stated that she had had jaundice at five years of age. Her past history was essentially negative other than the jaundice, as was her family history.

Physical examination revealed that she was quite tender over the gall-bladder, less so over the appendiceal region. Exhaustive studies of her gastrointestinal tract revealed no pathology to account for her symptoms, and in spite of management these attacks continued to recur. She developed some dizziness. This vertigo became a prominent symptom in her clinical picture. Exhaustive ophthalmological, otological and neurological examinations by very competent consultants failed to enlighten us as to the possible source of her symptoms and complaints. And yet, in spite of it all symptoms persisted. With all these findings essentially negative there still must be some source for these manifestations, and she was therefore told to see a psycho-analyst who found a very definite incompatibility at home, associated with a fear of pregnancy. Following management in the hands of the psycho-analyst her symptoms have entirely disappeared. The patient is exceedingly happy and is very comfortable.

A similar case to this is a patient who has had a diarrhea for years and years and years, ever since she has been married. The most exhaustive search for the cause of the diarrhea from a gastro-intestinal standpoint revealed nothing. There were no allergic manifestations to serve as etiologic factors. Feeling that there must be some reason for these gastro-intestinal upsets, she was also referred to a psycho-analyst. He found that there was incompatibility in the home and some brutality on the part of the husband in presumably intelligent surroundings. Since these have been corrected, she is entirely free from her gastro-intestinal symptoms. This further emphasizes how frequently large bowel disturbances may be on the so-called "functional basis." This observation has been made so repeatedly that even the laity are acquainted with the influence of nervous disturbances on the so-called "stomach and bowel."

I have repeatedly called to your attention the numerous cases of cardiac involvement which come in complaining mainly of gastro-intestinal symptoms. When one realizes the marked hyperemia of the liver and the hyperemia of the gastro-intestinal tract, is it any wonder that these patients complain so frequently of abdominal symptoms? These manifestations

may become so acute that to all intents and purposes they simulate an acute surgical abdomen, particularly resembling that of acute gallbladder. And to carry the clinical picture a little further, these patients may frequently develop jaundice and it has been explained by some that this bilirubinemia is associated with infarction in the lung, and the increased amount of serum bilirubin liberated is just enough to be retained in the blood stream due to the rise of the liver threshold for the secretion of bilirubin. So one should be careful in coming to too rapid a conclusion regarding a surgical abdomen in the presence of a decompensated heart. Coincident with the improvement of the cardiac manifestations, so do the gastrointestinal symptoms subside. Similarly, one sees gastro-intestinal manifestations in disturbances of the kidney.

Low grade nephritides or chronic uremia may have no symptoms at all pointing to the urinary tract. The entire clinical picture may resemble that of a disturbance in the abdomen. I do not emphasize at this time those acute manifestations of kidney pathology which resemble acute manifestations in the abdomen, but I am sure they have been sufficiently emphasized to you in your other courses. Here again under therapeutic management in those cases which respond to our best known methods of therapy at the present time in our attack on renal disease, the abdominal picture completely subsides. These manifestations do not resemble any particular disease of any one organ and it is for that reason they offer some difficulty in diagnosis from the abdominal viewpoint. How often does one see in women complaints which they think are entirely digestive in origin that may be associated with pathology in or about the pelvic organs. Just recently there was called to my attention a young woman who had been repeatedly treated for various diseases of the gastro-intestinal tract which on very careful search I found nothing which would account for her gastro-intestinal symptoms. But I did find a very large, incarcerated ovarian cyst which, when removed, entirely cleared up clinical manifesta-

tions. Tubal and uterine pathology are equally responsible for upper abdominal manifestations.

Now, while I admit that maybe I have left out some systemic manifestations which cause abdominal disturbance, I have tried to bring home to you this morning the one important outstanding clinical fact, that the clinician should never be gullible; the fact that a patient complains of his or her stomach is no reason at all for you not to read between the lines and find out if there is remotely some other cause for those symptoms. When examining a patient for gastro-intestinal symptoms, you begin at the head and go right down to the feet as you would in any other type of examination and then begin to correlate your abdominal findings with findings elsewhere. Then you can make an exhaustive study from the laboratory and x-ray standpoints to see if there is enough pathology in the gastro-intestinal tract to account for the symptoms. Finding that pathology lacking, it may be necessary for you to search further as to the possible cause of the disturbance. It is only by this type of clinical practice you are able to arrive at a more accurate conclusion and a more accurate diagnosis in any one given case.





## CLINIC OF DRS. SOLOMON STROUSE AND HERBERT F. BINSWANGER

MICHAEL REESE HOSPITAL

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### TREATMENT OF COMA

SINCE coma is a symptom of many underlying conditions it is axiomatic to say that the treatment of coma must depend on the nature of the etiologic factors involved. Therefore it would be unwise to discuss treatment without at least a cursory analysis of the causes. In the diagnostic studies made on any given case of coma we frequently find that the diagnostic procedure also becomes good therapy. It will be seen in the course of our subsequent analysis that not infrequently the diagnosis and therapy are virtually the same.

Even assuming the necessity for an etiologic diagnosis in a case of coma, it must be faced at the outset that not all cases lend themselves to proper diagnosis. Sometimes the wise physician must stand aside for the march of time to clear the picture. During this period, however, the same diagnostic procedures should be adopted as would apply to any other kind of a case. Despite the fact that the patient is in coma, all available history obtainable from family or friends should be accumulated. At times this may mean considerable effort on the part of the physician, but the results usually are worth the effort. Emphasis should be placed on this point because the natural tendency in a case of coma is to act. As an illustration of the value of obtaining a history, one may cite the case of a woman picked up in a department store and brought into a hospital apparently with hemiplegia. Without any clue obtainable from her it was impossible to make a diagnosis until the family arrived and informed the physician

that she was a patient of one of us (S. S.) and taking insulin. When we were called in the next day we found that instead of taking 8 units of insulin she had taken 80.

The alcohol breath which may be found in so many cases of coma is in itself of little value, but if an attendant makes the statement that the patient never drank or the opposite statement, that the patient is a confirmed drunkard, much diagnostic and therapeutic help is obtained.

Again, before attempting any therapy a most careful physical examination is indicated, and even at the risk of emphasizing the obvious, we believe it necessary to stress the extreme value of accurate observation, particularly of the skin, mucous membrane, and the type of breathing. The diagnosis may be made in certain cases of coma by the presence or absence of cyanosis, Cheyne-Stokes breathing, the Kussmaul breathing or a slow or shallow breathing. Signs of external injury demonstrable by blood coming from the nose, mouth, eyes or ears, injury to the scalp, and the signs of trauma anywhere else in the body must be carefully looked for. The odor of the breath, of which we have previously spoken, may or may not be of importance but must be carefully noted. It is not always possible particularly in the presence of mouth infection to distinguish types of odor in the breath.

A study of the reflexes and of muscle tone and all the other tests which go to make a good neurologic examination are of course indicated. Whatever is found from this examination must be carefully analyzed. The absence of reflexes, for instance, may be the result of shock rather than a sign of prime importance. Pin-point pupils of opium poisoning as contrasted to the dilated pupils associated with barbitol poisoning may form a decisive point in differential diagnosis. The finding of an enlarged heart and fibrillating pulse in the case of coma suggests naturally a cerebral embolus, and a fast feeble pulse may indicate the failing heart of hemorrhage, coronary disease, or may be a terminal finding.

In the treatment of a case of coma the presence of sugar, acetone or albumin is of obvious significance, but it should be

emphasized that no one of these substances is absolutely specific. Sugar may occur not only in diabetes, but in almost any type of brain injury. Acetone while it may indicate diabetic acidosis, especially when associated with other clinical signs, may occur in starvation and be of absolutely no diagnostic value. Albuminuria likewise cannot be interpreted entirely in association with other physical findings. The urine in all cases of coma should be saved so that if there is other evidence to suggest poison, the specific poison may be looked for.

Interpretation of the blood pressure will depend to a great extent on any information obtainable concerning the preceding state of the blood pressure. If a patient is seen with peripheral arteriosclerosis and a low pressure and we are told by the family that he previously had a high blood pressure, we immediately must suspect a cerebral accident.

No better illustration of the point mentioned earlier regarding the relationship between diagnosis and therapy can be cited than gastric lavage. Perhaps done primarily for diagnostic purposes, the diagnostic test immediately becomes a therapeutic procedure.

It is our belief that lumbar puncture may be used as a routine procedure, either diagnostically or therapeutically, and may clear up the whole picture.

From a therapeutic point of view coma cases may be divided into four groups: (1) Those requiring immediate trephining, (2) those requiring stomach lavage and antidotes for drugs or other poisons, (3) those requiring specific treatment as in diabetic coma or a real case of poisoning, and (4) those requiring rest and watchful waiting.

Fortunately only a few cases require immediate trephining and they are the ones which show evidence of increased intracranial pressure, such as increase in blood pressure, with slow pulse, nausea and vomiting, and choked disk. Such cases usually are either traumatic or may be due to brain tumor, and usually a trephining operation is then performed. If the increased pressure is due to cerebral hemorrhage and if this

hemorrhage arises from the middle meningeal artery, this artery may be ligated.

The first treatment of cases due to poisoning is lavage of the stomach. If the specific drug can be found antidotes should immediately be given. In cases of morphine and barbitol poisoning, potassium permanganate is used in the lavage solution. If mercury is the etiologic factor milk or egg-white should be used.

Coal gas poisoning is usually identified by the cherry red color of the patient and specific changes in the spectroscopic bands. Treatment by oxygen and carbon dioxide inhalations is urgent, and according to some, intravenous injections of methylene blue may be helpful.

In not all cases can a specific drug be identified and certain general measures are indicated. A strong cathartic, such as Epsom salts or castor oil, should be given after the lavage. Stimulants, such as caffeine, strychnine and coramine, may be of urgent need. Intravenous glucose is a rapid method of stimulating urinary secretion. This may be used in 5 to 10 per cent solution or even stronger. In all cases the patient should be kept warm by blankets, hot-water bags or electric pad, and should be turned frequently from side to side. Artificial respiration may be compulsory in some cases. The feeding problem is not easy but an effort should be made to maintain nourishment. Rectal feeding is not very satisfactory but has to be used. A nasal catheter may have to be used, especially in cases of poisoning from caustic drugs. The nasal catheter is generally speaking the best means at our command at present.

In the third group of cases, namely, those with a specific etiology, we find our most satisfactory results in diabetic coma. In this condition it is necessary constantly to keep in mind the principle for which one is striving. For instance, the height of the blood sugar or even the exact amount found in the urine is not important because the coma depends on acetone bodies rather than on glycosuria. In the treatment of diabetic coma insulin is a specific and provided there are no

complications will in the majority of cases result in restoring the patient to consciousness. Although insulin can never be given blindly, it is always safe to give a comparatively large dose in a proved case of diabetic coma, and in general practice where the controls may not be as accurate as they would be in an institution, we believe it is safer to combine insulin with glucose in some form. To be more specific, the initial dose may be anywhere from 30 to 50 or 60 units without bothering about extra glucose. More than 60 units at a single dose is of little value. The patient's clinical condition is watched and the urine studied, particularly from the standpoint of sugar and acetone. The further treatment is determined by the course of events. The urine should be examined every two hours, even if it is necessary to catheterize the patient. If at the end of the first two hours there are signs of diminishing acidosis the amount of insulin may be reduced to 20 to 40 units, but at this time we believe it is wise to add glucose either in the form of hypodermoclysis (2.5 per cent solution) or by mouth if the patient is now able to drink orange juice or milk. As the acidosis clears up the insulin is further reduced. If despite large initial doses there are no signs of improvement more insulin should be used, but this should be controlled not only by urinalysis but by blood sugar studies. The careless use of insulin must be distinguished from the use of large doses, because the careless use of too large doses may result in hypoglycemia and coma due to this condition. We have seen this happen and we believe that it is a fairly common occurrence which must be guarded against.

General measures are of extreme importance in diabetic coma. The patient must be kept warm, the bowels should be emptied by a cleansing enema, and particularly, dehydration, which is so commonly a concomitant symptom, must be combated. Hypodermoclysis should be instituted immediately and should be continued until the dehydration is controlled. The heart bears a terrific burden and must constantly be watched, particularly in older people. When the treatment of the dehydration does not improve the cardiac condition,

most drastic treatment is indicated. During and immediately after the coma no great attention need be paid to the control of the diet, since carbohydrates are definitely indicated during this period. However, as soon as the patient passes the borderline, the usual principles of dietetic therapy are applicable.

In contrast to the dramatic specific therapy of diabetic coma, the case of uremic poisoning offers only certain general therapeutic principles. Perhaps the intravenous injection of glucose solution, 200 to 300 cc. of a 10 to 25 per cent solution at intervals of a few hours, offers the best therapeutic hope. Small but repeated transfusions preceded perhaps by venesection have given good results in some hands. The use of stimulating drugs, such as digitalis or caffeine, are certainly indicated when the heart or peripheral circulation fails. Some investigators have claimed rather brilliant results from the use of intravenous solution of 40 per cent urea given in 50 cc. doses every eight hours. We have not seen as good results from this procedure as have been reported in the literature.

In the fourth group belong practically all cases of coma due to accidents to the cerebral blood vessels. Much has been written about the diagnosis and treatment of these conditions. Our own experience suggests that at times it is almost impossible to differentiate cerebral hemorrhage from thrombosis and a careful analysis of our results suggests that the less interfering therapy is used the better the prognosis. At the onset it is impossible to predict the outcome. What looks like a mild cerebral accident may progress steadily downhill, and what starts off as a wild outburst may quiet down. It has been our policy not to do a venesection, lumbar puncture, or move the patient. We believe that the patient should be kept where he is whenever possible, at least for the first twenty-four hours, and nothing whatever but careful watching and nursing is indicated. In the presence of extreme restlessness or convulsive seizures morphine or opium derivative is indicated to obtain the essential quiet and rest. After the first twenty-four hours the general condition of the patient requires

attention. Dehydration is to be avoided. The bowels must receive attention and, if necessary, stimulation by caffeine or digitalis given.

Not all possible causes of coma have been included in this discussion nor has anything been said about the problems involved when the patient has one disease and gets coma from something else. The diabetic may go on an alcohol spree and when he is seen by the doctor it is not an easy matter to decide whether he is suffering from alcoholism or from diabetic coma. The patient with a known duodenal ulcer may take an overdose of a drug and it will require keen diagnostic judgment to decide whether the coma is due to cerebral anemia from hemorrhage or to a drug. The type of case which will be most common in one locality or one institution may be less common in another. Alcoholism, for instance, is very rare at Michael Reese Hospital, while in the public institutions it is apt to be one of the commonest causes of coma.



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## CLINIC OF DR. WILLIAM A. BRAMS

### MICHAEL REESE HOSPITAL

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#### VENOUS PRESSURE

EVERY clinician is familiar with the close relationship which exists between arterial blood pressure and myocardial function of the left side of the heart. It is not so generally recognized that venous pressure is a very reliable index of functional capacity of the right side of the heart with the result that estimation of pressure in the peripheral veins has not as yet become a popular procedure in clinical medicine. It cannot be said that determination of venous pressure is a recent development, for Stephen Hales in 1733 reported his experiments in these words: "In December I laid a common Field Gate on the Ground, with some Straw upon it, on which a white Mare was cast on her right side, and in that Posture bound fast to the gate; she was fourteen Hands and three inches high; lean, tho' not to a great Degree, and about ten or twelve Years old. . . . Then laying open the left Jugular Vein, I fixed to that part of it which comes from the Head, a Glass Tube, which was four Feet, and two Inches long. The Blood rose in it, in three or four Seconds of Time, about a Foot, and then was stationary for two or three Seconds; etc., etc."

Nor can it be said that modern clinical methods for estimating venous pressure are difficult or inexact. Practically all procedures may be classified as either indirect or direct. Most of the indirect methods are based on the principle of compressing a visible, superficial vein in the skin by means of a transparent air chamber and reading off on a water manometer the pressure necessary to obliterate completely the vein under examination. These methods are used widely and are easy to perform but considerable experience is needed to recog-

nize the end point of compression, a change which is not always sharply defined.

We prefer a direct method because it is more accurate and the end point is always distinct. A simple instrument designed by Dr. J. S. Golden and myself overcomes the usual objections raised against direct methods, namely, that the hollow needle may become plugged by a clot and that prolonged observations are impractical. Our apparatus consists of a small metal reservoir and a water manometer, both being connected to a small hollow needle by a glass T tube and suitable rubber tubing. The entire instrument is carried in a small metal box, in which it may be autoclaved and both the reservoir and manometer may be easily attached to the opened cover when readings are to be made. Sterile 3 per cent sodium citrate solution is poured into the reservoir and manometer and the fluid is allowed to fill the tubing and needle, care being taken to expel all air bubbles. The patient is kept in a recumbent or semirecumbent position with the arm well abducted for at least fifteen minutes and the level of the auricle is marked on the side of the thorax according to the suggestion of Eyster. The hollow needle is then introduced into the cubital vein and citrate solution from the manometer tube is permitted to flow into the vein until the level of the solution in the manometer tube becomes stabilized. The height of this level above that of the auricle represents the peripheral venous pressure. The apparatus may be maintained in faultless working order for three to four hours without discomfort to the patient and without removal of the needle from the vein by permitting a few drops of citrate solution from the reservoir to flow through the needle into the vein every five minutes.

We have adopted a range of 5 to 10 cc. of citrate solution above the level of the auricle as the normal venous pressure when taken according to our method. Abnormal variations are found in many conditions, but we shall briefly describe our clinical experience with venous pressure in cardiac failure and with certain therapeutic measures used in combating this condition.

It must be stated at the outset that an abnormal level of venous pressure is not a sign of any particular valvular defect or special anatomical lesion. It does furnish very important information as to the myocardial capacity of the right side of the heart. Any condition which leads to failure of the right side of the heart causes a rise in peripheral venous pressure but so-called "pure, left sided failure" causes no such change. Hence, the procedure is of value in distinguishing these two forms of failure in which the treatment is also different. It is of further advantage to estimate venous pressure in instances of right sided failure because cyanosis and the apparent size of the cervical veins may at times be misleading. For instance, much more carbon dioxide in the blood and oxygen deficiency will be necessary in cases of anemia to produce a given degree of cyanosis than in normal persons and much less in patients with an excessive number of red blood cells. This is merely an example of the extracardiac factors which may have an important relation to the degree of cyanosis. We have observed that the apparent degree of engorgement of the cervical veins may be deceptive. Large cervical veins may be due chiefly to emaciation or to local obstruction. Measurement of venous pressure in such instances will furnish much more reliable information than mere inspection.

Elevation of venous pressure in a patient known to have cardiac disease but who is apparently in a good state of compensation will sometimes serve as a warning of impending failure. It may, in fact, be the earliest sign of impending cardiac defeat in a patient in whom such a state is not suspected. The information gained by repeatedly estimating venous pressure may be of value in following the progress of right sided failure. Tendency of venous pressure to fall usually means improvement while persistence of a high level or tendency to rise frequently presages complete cardiac defeat. The results of treatment may also be followed by such repeated observations and great value is placed by some on estimation of venous pressure as a guide for the performance of venesection in instances where venous pressure is high. Dr.

J. S. Golden and I were interested in the value of so-called "bloodless venesection" in patients with heart failure and high venous pressure. As is well known, the procedure consists of constricting all four limbs near the trunk; sufficient compression being applied to permit inflow of blood into the limb while outflow via the veins is prevented. It was thus hoped to relieve the heart of a certain quantity of blood by imprisoning blood in the limbs and to accomplish this without actual loss of blood, since hemorrhage is not always well borne by patients with heart disease. We permitted the constrictors to remain in position for thirty minutes after control readings were taken and measured venous pressure in one unobstructed limb at intervals of five minutes. Blood pressure was also measured and the pulse rate counted at the same intervals. We could find no change in venous or arterial pressure or pulse rate, although the same patients showed an immediate and partially sustained drop in venous pressure after ordinary blood letting. We have, consequently, omitted this procedure from our therapeutic armamentarium.

Dr. Golden and I performed a series of experiments to determine the effect of ordinary blood letting on patients with varying degrees of cardiac failure with and without elevated venous pressure. We found no change in the pulse rate and only a transient fall in arterial blood pressure, but venous pressure fell in every instance. The fall in venous pressure was marked in many instances but nearly always returned about halfway toward the previous level within an hour. We have watched the ultimate course of these patients and believe that venesection may be of benefit in some cases of right sided failure with high venous pressure, but we cannot share in the enthusiasm of ardent advocates of venesection. We have followed many patients after venesection and are convinced that more conservative measures would have been of nearly equal benefit. It is possible that our patients had very little cardiac reserve, but we are inclined to rely on digitalis, sedatives and diuretics and to advise venesection only occasionally in right sided cardiac failure.

## CLINIC OF DR. HEYWORTH N. SANFORD

### PRESBYTERIAN HOSPITAL

#### THE IMMUNIZATION OF INFANTS AND YOUNG CHILDREN AGAINST INFECTIOUS DISEASES

ONE of the most important fields of pediatric procedure exists in the immunization of infants and children against infectious diseases. This has been so popularized among the general public that at the present time most parents are more than anxious to cooperate with the physician on these measures. It is well, however, to realize that not all infectious diseases can be prevented by definite control measures. Unless this is made clear to anxious parents, extravagant promises of disease prevention will cause doubts to arise in the public's mind that will destroy all confidence in preventive pediatrics. It is well, therefore, to divide these diseases into two groups. First, those in which we have a definite method of prevention and immunization, and second, those in which we have a partial or limited method of control.

#### THOSE COMMUNICABLE DISEASES FOR WHICH THERE IS A DEFINITE METHOD OF PREVENTION AND IMMUNIZATION

**Smallpox.**—During epidemics of smallpox, vaccination should be performed at any age. This includes infants in the newborn period. As a general public health procedure, infants should be vaccinated from the sixth to the twelfth month of life, or not later than the eighteenth month of life. The reasons for doing so at this time are that they are given protection from the disease (there is hardly any inherited immunity), the reactions are almost negligible at this age, and lastly, post-vaccinal encephalitis hardly ever occurs under eighteen months of age.

In the absence of an epidemic, it is usually well to postpone vaccinating children afflicted with such skin diseases as eczema, impetigo, and furunculosis. Infants suffering from severe gastro-intestinal upsets, or marked malnutrition may be spared the added burden of vaccination until they are stronger. While it is probably quite hypothetical, I believe that the best time for vaccination is in the late spring, early summer and fall. Obviously the hot months are depressing and excessive perspiration may cause scratching of the pustule and secondary infection. During the winter and early spring the child may suffer from a respiratory infection or contagious disease. While most parents are intelligent enough to know that these diseases are not caused by the vaccination, still in the back of their minds they will wonder if the vaccination did not lower the child's resistance to the disease.

Vaccination may be done on any skin surface. The preferred site in boys is at the point over the insertion of the deltoid muscle on the left arm. In girls, the outer aspects of the left thigh, at a point two thirds of the way from the knee to the hip is the best location. One is accustomed to looking for a scar in these locations in examinations, and there is no reason for placing the vaccination in bizarre localities.

The site of vaccination should be thoroughly washed with acetone. Other antiseptics may destroy the virus. A drop of virus is placed in the center of the cleansed area. Holding a small sterile needle at an angle of 20 degrees from the skin surface, the point of the needle is pressed into the skin through the drop about ten times. Obviously these pressure points should be in the same locality. No blood or serum should be drawn. The excess of virus is now wiped off with a piece of sterile gauze.

There is some difference of opinion as to the advisability of putting a dressing over the inoculation. It is permissible to use no dressing. Certainly tight constricting bandages and shields should be strictly avoided. I always put one thickness of sterile gauze over the point of inoculation very loosely with a piece of tape. The mother is told to remove this next morn-

ing and put nothing more on it until the pustule appears. She is then told to place a similar piece of gauze on the pustule, and to change it daily unless the pustule breaks and sticks to the gauze. If this happens the gauze is not removed. No tub bath is given the child from the time the pustule appears until the scab is on firmly. The mother is warned that a papule usually appears on the third to fifth day. In another day this becomes a vesicle and the next day a pustule with a swollen red area around it. At about the sixth day there is frequently some fever and loss of appetite. Mothers are told to report one week after vaccination for inspection and further instructions.

Reactions will fall into three groups. Successful primary vaccinations in which a pustule is present on the seventh day; an unsuccessful vaccination shows no reaction to the virus and confers no protection against smallpox. Those who fail to react after a primary vaccination with the production of a pustule should be revaccinated after two weeks. Children revaccinated after a previously successful result may show a reddened, inflamed macular or maculopapular area at the vaccination site at about forty-eight hours. This is evidence of persistent immunity from the previous vaccination.

The complications of vaccination are secondary infection, generalized vaccina, autovaccination and postvaccinal encephalitis. If the procedure is carried out as outlined, secondary infections are very uncommon. They were more common when shields and tight bandages were used. They can be told by excessive swelling, abscess formations and lymphatic enlargement. Secondary infection of the pustule may be treated by cleansing the pustule with ether and painting with a mild antiseptic as gentian violet or mercurochrome. Abscesses should be treated surgically with wet dressings.

Generalized vaccina occasionally happens. It varies from scattered pustules around the primary lesion to scattered papules and vesicles over the entire body. The child may have several degrees of temperature and be quite prostrated. There is nothing to do for these children except to give anti-



pyretics for the temperature. The prognosis is excellent and recovery rapid. Those children who have eczema or delicate skins appear more likely to have such reactions.

Autovaccination is caused by not wiping off the excess of vaccine which the child scratches and carries to other parts of the body, or by scratching an uncovered pustule. The most common points are the lips, cheeks or eyelids. They follow the course of the original vaccination. Nothing can be done and they are unimportant with the exception of the eyelid or cornea. This is very serious and may cause loss of the eye. Call an ophthalmologist into consultation immediately if this happens.

Postvaccinal encephalitis has received considerable attention abroad. In this country only 75 cases have been reported. Considering the number of antismallpox vaccinations performed yearly, this number is very small. In the countries where postvaccinal encephalitis occurred, it affected children mostly of school age; only rarely has a case occurred in infants under two years. An exception is Germany, where nearly all cases are between one and two years. However, most children in Germany are vaccinated at that time.

The symptoms appear suddenly, on the tenth to the thirteenth day following vaccination. Fever of  $104^{\circ}$  F., vomiting, headache, stupor and positive Babinsky are the most important symptoms. The course is stormy and the prognosis is grave. The mortality is 40 per cent. Recovery, when it takes place, is usually rapid and complete. Besides the usual treatment for encephalitis, the child should be given blood serum from a recently vaccinated person.

As a preventive measure for vaccine encephalitis, the following principles should be used in vaccination. Primary vaccination should be done early in life, during the first year if possible. No person should be vaccinated unless in perfect health. Mass vaccinations are to be avoided. In Holland, most cases of postvaccinal encephalitis occurred in March and April. Multiple scarification and cross hatching were condemned by the English committee. Armstrong recom-

mends that primary vaccinations, especially after the first year of life, be deferred until immunization against diphtheria or other diseases has been accomplished, as this preliminary exercise of the immunity or defense forces may lead to a more efficient antiviral response.

**Diphtheria.**—Immunization against diphtheria should be a routine procedure. Most infants have a natural immunity to diphtheria at birth that begins to fall off at about the sixth month. For this reason it has been advocated that immunization should be begun at this time. Certainly in infants living in slum surroundings, more liable to infectious contacts, this is advisable. In the average infant that has medical supervision, I do not think it is advisable to immunize before one year of age, but it should be routine at this time. Certainly in babies of this type, diphtheria under eighteen months of age is quite uncommon. Furthermore, the work of Greengard indicates that the passive immunity in young infants interferes with the development of antitoxin in response to vaccination with diphtheria toxoid. The only infant in my experience that died of diphtheria under fifteen months of age had received toxoid at six months of life.

Immunization should be routine at one year and advocated up to ten years. A Schick test preliminary to immunization is unnecessary for children less than seven years of age. For older children it is desirable to determine the need for immunization.

Toxoid should be employed for children under seven years of age. At the present time most men are using two doses of 1 cc. each, at not less than two- nor more than four-week intervals. Some give three doses which probably gives a higher immunity, but inasmuch as two doses of 1 cc. each at two- to four-week intervals give a 90 to 95 per cent immunity, this hardly seems necessary. The one dose alum precipitated toxoid in amounts of 0.5 to 1 cc. (varying with different preparations) may supplant the other toxoid. It has the advantage of one injection because of slow absorption. It appears to be very successful in children under seven years

of age. It should be used with great care in older children because of local reactions.

The arm over the deltoid region is cleansed with soap, water and alcohol. The toxoid is given in a sterile syringe and needle subcutaneously. Be sure that there are no air bubbles in the syringe, and that the needle is wiped dry, also do not use formaldehyde toxoid solution unless it is perfectly clear. The injection site is covered with a sterile gauze bandage, removed the next morning. The mother can be assured that there will be no reaction at this age. The second injection is given in the other arm in two to four weeks.

Immunization with toxoid should never be done for a child of over seven years without first testing their reaction to it. This is done by injecting 0.1 cc. of toxoid intradermally. If within three days an area of redness measuring more than 10 mm. develops, either one of two procedures may be used. The first is to use toxoid, giving one dose of 0.2 cc. subcutaneously followed in two weeks by a second dose of 0.5 cc. and in two more weeks by a third dose of 1 cc. In the event of a reaction after the first dose, the amounts subsequently injected should be cautiously increased or the same dosage repeated. Immunity may be produced by three injections of as little as 0.2 cc. each. The second method is to use toxin-antitoxin mixture, which generally produces less reaction in older individuals. Three successive injections of toxin-antitoxin mixture, in amounts of 1 cc. each, can be given subcutaneously, from one to two weeks apart.

Diphtheria immunization is worthless unless it is followed up with the Schick test. While with the two-dose method of toxoid, 90 to 95 per cent of children will become immune within three months, the five or ten children who are not immune could spoil the effect of the entire procedure by raising doubts in the mother's mind as to the reliability of the method.

Diphtheria toxin for the Schick test is supplied in ten test ampules. The ampules are 1 cc. each and contain diluted toxin in peptone solution. They are stable for a period of months, as stamped on the bottle, if precautions are used.

These consist in keeping the bottle in the ice-box when not in use, and thoroughly wiping off the rubber top with alcohol before piercing with the needle. Obviously the needle and syringe should be sterile. Use a syringe graduated in 0.1 cc. and a fine needle (26 gauge) with a rounded point. Cleanse the flexor surface of the arm with soap and water and alcohol and inject 0.1 cc. of the diluted toxoid intradermally. A superficial bleb should result, through which the hair follicles can be seen. Cover this with a piece of sterile gauze, to be removed the next morning.

The test is read in forty-eight to seventy-two hours. A positive reaction is shown by redness of the skin covering an area of over 10 mm. in diameter. Positive reactions usually stay red for several days, turn brown and scale over the point of injection. A negative reaction shows a red area less than 10 mm. Schick tests have been made on so many children with such conformity of results, that the mother can be assured that her child is now immune to diphtheria. As a further safeguard, it should be recommended that the child be re-Schicked on entering school, or in the presence of an epidemic. Some children have been known to lose their immunity in four or five years. If a positive reaction is obtained, one may wait another three months and repeat the Schick test, or give another 1 cc. of toxoid at once, and re-Schick at three months. Some children will no doubt become negative in another three months, but I always give one more dose of toxoid to be safe. Schick reactions are uniformly negative after the third dose of toxoid.

It must be emphasized that immunization does not take place for three months and none of these methods should be relied upon for active immunity in the presence of diphtheria. In such cases 1000 units of diphtheria antitoxin should be given intramuscularly. Remember that this is a horse serum and the child may be sensitive to it. All children with a history of eczema, asthma, or any sensitivity, or who have had any horse serum before (including toxin-antitoxin mixtures) should be tested for sensitivity before giving the injection, by injecting intracutaneously 0.1 cc. of a  $\frac{1}{10}$  or  $\frac{1}{100}$  dilution

of antitoxin. If no wheal or marked zone of erythema appears within thirty minutes, the full dose may be given. If such a reaction appears, the antitoxin should be given in divided amounts beginning with 1 cc. in  $\frac{1}{100}$  dilution with saline solution. At intervals of thirty minutes increasing amounts may be given until the entire amount is completed. This should be given in an extremity, so that rapid absorption can be impeded by a tourniquet if an immediate reaction issues. In case of a severe reaction, 3 to 6 minims of a  $\frac{1}{1000}$  epinephrine solution should be given subcutaneously.

**Typhoid Fever.**—While immunization against typhoid fever is a definite prophylactic procedure, it is not necessary in most communities for universal application. Its use should be restricted to those communities where typhoid incidence is great and particularly if a trip is planned to such a region. This applies particularly to Europe and the Orient, or to rural communities in this country where the water supply is questionable.

Immunization could probably be given to the child at any age. Certainly at one year of life it would be satisfactory. The vaccine given for adults is in amounts of 0.5 cc. for the first dose and 1 cc. for the second and third doses. There is no definite amount recommended for children. I usually give children over eight a full adult dose and under eight years two thirds of the adult dose. The injections are given subcutaneously in the deltoid region at one-week intervals. As a rule, children have no reactions. It probably takes about three months to establish an immunity. There is no simple laboratory test for determining typhoid immunity, but it is assumed that immunity lasts at least two years. If protection is to be assured beyond this time, a second course of injections should be given, or one dose may be given each year following the original course of three.

**Tetanus.**—Tetanus antitoxin should be always used prophylactically in all cases in which a wound is contaminated with horse manure or human excreta. This, therefore, includes all wounds of the street, in gardens, or any spot where

street dirt may have been trampled. Also all wounds contaminated with water at bathing beaches, or industrial injuries. It is particularly indicated in puncture wounds or wounds about the head. The prophylactic dose is 1500 units injected subcutaneously. Remember that this is a horse serum and the precaution mentioned under diphtheria should be followed.

At the present time there is much work being done on vaccination against tetanus, which may develop into a standard procedure later. Ramon has been using an anatoxin mixture in French soldiers with apparent success. Bergey and Etries in this country recommend one injection of a 1 cc. alum precipitated tetanus toxoid for immunization. This is given in one injection and gives an immunity in three to six months. They claim there are no reactions. At present, however, only antitoxin should be relied on.

#### THOSE DISEASES IN WHICH PREVENTATIVE MEASURES ARE LIMITED OR INDEFINITE

In these diseases the mother should be told that the methods of immunization are not perfect. It is folly and detrimental to the public faith in preventive pediatrics to make extravagant claims as to immunizing children for these conditions.

**Scarlet Fever.**—Natural immunity is found in many children, and a considerable number of adults. Inherited immunity is present in the newborn if the mother is immune, and lasts in one half the children for six months and in one third for twelve months. Clinically scarlet fever is uncommon under two years. For this reason infants may be Dick tested at any time, preferably after one year. I test routinely between eighteen months and two years.

Dick test material is obtainable in 10-test ampules and 100-test ampules. The 10-test ampules are glass topped and must be used at once. The 100-test ampules have a rubber top and if care is used as outlined with Schick test material (use acetone to sterilize top, not alcohol), they may be used until the expiration period stamped on the bottle. Great care

must be used in performing the Dick test. Use a syringe graduated in 0.1 cc. and a 26-gauge needle with a round end. Boil the syringe and needle in distilled water. Use no alcohol. Cleanse the skin with acetone. Expel at least 0.1 cc. of the scarlet fever toxin from the needle before using. Inject accurately 0.1 cc. of the scarlet fever toxin intradermally. Injections must be intradermal as a subcutaneous injection may show negative results in a positive subject. Cover with a sterile gauze bandage and read in twenty to twenty-four hours (not later). Unlike the Schick test there will always be some erythema. If the area of redness measures over 10 mm. in diameter, the test is positive.

If the test is negative, it may be assumed that the child is immune to scarlet fever. However, it must be remembered that this test is not perfectly reliable. Persons with negative Dick tests have been known to contract scarlet fever. The mother should be warned of this and told to have the child retested in the presence of a scarlet fever contact, or epidemic or in any case in two or three years.

If the test is positive, all of the factors that enter into the situation should be explained to the mother. Nursing groups, personnel of contagious hospitals and orphanages, or groups intimately exposed to scarlet fever should be protected. The Committee on Prophylactic Procedures Against Communicable Diseases of the American Academy of Pediatrics does not recommend active immunization by scarlet fever streptococcic toxin as a general public health procedure because local and general reactions are frequent in adults and not altogether absent in children. Also the degree and duration of the immunity have not been definitely established. However, the degree of reaction is certainly not as bad as a case of scarlet fever. I believe that the principal argument against it is the degree and duration of immunity. These facts should all be laid before the mother and let her decide. I certainly would not force the immunization against her desire not to have it.

Active immunization, if decided upon, consists in the injection of five increasing doses of scarlet fever streptococcus

toxin at weekly intervals. These injections are made subcutaneously as with the diphtheria toxoid. This material is put up in 1-cc. vials and are numbered one to five. Great care must be taken to give these doses in order as they increase rapidly in toxin and would cause serious reactions if given out of order.

It is stated that about 10 per cent of susceptibles will show general reactions after the first dose and about the same number following the last dose. From my own experience, I would say that 30 per cent was a closer figure. These reactions are a temperature up to 102° F., vomiting, diarrhea, and headache. These come on in a few hours and last about twenty-four hours. They may be treated symptomatically. I find the vomiting most troublesome. It may be necessary to withhold all food and give only tablespoonfuls of water for twenty-four hours to control it. In the presence of severe reactions it is best to divide the next dose of toxin, and give it the following week. If there are no reactions, the usual routine can then be followed.

Two weeks after the last dose of toxin, repeat the Dick test with 0.1 cc. of toxin in the right arm and 0.2 cc. in the left arm. If either test is positive, repeat the fifth dose, after which 95 per cent of the susceptibles will become negative. The mother should be instructed to have the Dick test repeated again in one or two years, or in the presence of a contact or epidemic.

This active immunization, of course, takes at least five weeks and is valueless for a susceptible contact. For these children, convalescent scarlet fever serum has been recommended for passive protection. It is given intramuscularly in amounts of 10 to 20 cc. The evidence as to its reliability is inadequate, but it should cause no reactions and I think should be used if obtainable. Scarlet fever antitoxin is also used for passive immunization. Its use is frequently accompanied by unpleasant horse serum reactions and the evidence regarding its value is indefinite.

**Measles.**—There is no method for active protection



against measles. The disease may be prevented, or better, modified by the injection of blood serum of a person recently convalescent from the disease, or the blood serum of adults.

Human blood serum taken one to three weeks after the fever of measles has subsided should be used. When administered within five days after exposure in doses of 10 cc. intramuscularly it may protect against the disease. It usually lessens the severity of the disease in any case and should be used in children under three years of age, or those suffering from another disease, particularly a respiratory infection. Under ordinary circumstances, it is more desirable to produce modified measles than to protect completely. Ten cc. of convalescent serum given six to seven days after the child has been exposed produces partial protection. That is, measles develops in a mild form.

Thirty cc. of normal adult whole blood, or 20 cc. of normal adult serum, will produce somewhat the same effect as 10 cc. of convalescent serum. It probably is not as reliable due to differences in protective substances. Measles modified by convalescent serum or normal blood apparently produces a permanent immunity comparable to the disease. McKahn has advocated the use of placental extract. It is believed that 2 cc. injected on the sixth or seventh day after exposure will usually modify the disease. This method could be used in the absence of convalescent serum, or adult serum.

**Whooping Cough.**—A vaccine for the active immunization against whooping cough has been developed by Sauer. This vaccine differs from the older types in that it is prepared from fresh strongly hemolytic strains of *B. pertussis*, grown on medium made with freshly defibrinated human blood. This gives the advantage of more massive doses than with the older vaccines. It apparently gives considerable immunity. Sauer believes that the best age to give it is between the seventh and tenth months. If the child has been immunized against diphtheria or smallpox, several months should elapse before pertussis immunization.

It should be remembered that more evidence should be gathered on this procedure before it is adopted as a general

public health measure. Whooping cough is one disease for which the infant has no natural immunity, almost all of the mortality occurs in the first and second years of life, therefore, if the infant can be protected, it is highly desirable. It takes four months for immunity to develop from Sauer's vaccine, therefore, it would be necessary to give it quite early in life. Whether it is wise to immunize young infants in the face of possible reactions remains to be seen.

In regard to older children, or those younger who have been immunized against diphtheria and smallpox, it could be considered. The facts should be laid before the mother; that reactions occur, and that while probably the majority of children will become immune, there is no test at the present time to discover who has become immune and who has not. Therefore, immunity cannot be guaranteed. As it takes four months for immunity to develop, immunizations should not be given during an epidemic.

The injections are given subcutaneously at weekly intervals for three weeks. The initial dose is 1 cc. in each deltoid, the second 1.5 cc. in each triceps, and the third 1.5 cc. in each biceps. This makes a total dosage of 8 cc. The skin should be cleansed with soap, water and alcohol, and the syringe and needle boiled in distilled water for ten minutes.

Reactions when they occur may be general or local with a rise in temperature to 101° F. four to forty-eight hours after injection, and tenderness, redness and induration. Movable, subcutaneous nodules of induration may exist for a month. Usually no treatment of any kind is necessary nor any change in routine of injection.

There are several methods of prophylactic immunization employed for those exposed to the disease. The older vaccines containing 5 to 10 billion killed organisms per cubic centimeter are given subcutaneously in doses of 0.25, 0.5, 1, and 1.5 cc. at intervals of two to three days. Their efficiency is under much dispute.

Frawley has reported good results in the use of undenatured pertussis antigen for prophylaxis. The initial dose is 1 cc. given subcutaneously, followed by 2 cc. every other

day until 6 doses have been given. Human blood serum is used in the culture medium, and there seems to be very little local or general reaction.

Convalescent serum from patients recovering from whooping cough has been used in amounts of 10 cc. for children known to have been exposed to the disease. The evidence in regard to this is indefinite.

**Chickenpox and Mumps.**—Blood serum from recently convalescent individuals has been used for both these diseases. Their value is not absolutely proven and the indication for such use is infrequent due to the mildness of these infections.

**Poliomyelitis.**—Kolmer has developed a method of vaccination against poliomyelitis by giving a suspension of monkey spinal cord, from animals receiving an inoculation with sodium ricinolated virus. This is given in three increasing doses at weekly intervals. It has only been used on a few individuals and is not commercially available as yet.

For passive immunity convalescent serum and normal serum have been proposed during epidemics. Convalescent serum might be of value, but it is so limited in amount that it should be confined to the treatment of early cases. Normal serum and whole adult blood have been used in amounts similar to those used in measles immunization. The value of these has not been demonstrated, but they certainly can do no harm.

**Rabies.**—If a child is bitten or scratched by a dog (cats and monkeys can also have rabies), and the skin is broken, give vaccine if the animal is unknown, disappears, dies in less than ten days, is killed in less than ten days, or develops rabies. If it has a suspicious sickness, begin vaccine and observe. It is not necessary to give vaccine if the dog remains well. Contaminated bites should be cauterized with nitric acid. Head wounds are the most dangerous.

Different preparations are supplied, but all are usually emulsified rabbit cord, infected with a fixed killed virus. They are incapable of producing rabies as a result of the injection. The treatment consists of 14 daily injections given subcutaneously. In cases of extensive injury, or more than a suspicion of rabies, 21 to 28 injections should be employed.

## CLINIC OF DRS. JESSE R. GERSTLEY AND MEYER TEITELBAUM

MICHAEL REESE HOSPITAL AND NORTHWESTERN UNIVERSITY  
MEDICAL SCHOOL

### RICKETS: IS THERE A DIETETIC FACTOR?

THIS baby is seven months old. To all appearances he is normal. I will not take time to go over all points in the physical examination but simply note no abnormalities other than the barest suggestion of beading of the ribs. This is no more marked than in many babies pronounced physically normal. He has no craniotables nor Harrison's groove. He holds his head up well and makes very definite efforts at sitting up, although he does not accomplish the latter with complete facility. His gums are swollen and one of the lower central incisors is just coming through. Possibly in development he may be a few weeks behind what is considered a perfect average. However, the fact that he has been boarded in the hospital ever since his birth may be the explanation. Are these findings sufficient to justify a diagnosis of mild rickets?

The family and past histories are negative.

In previous clinics I have discussed "The Normal Infant" and also "Infant Nutrition." Do not be alarmed. This is no repetition. This baby is being demonstrated as an introduction to the subject of rickets.

During recent years the profession and the public have been almost overwhelmed with literature on rickets. I must confess that I do not quite understand the reason. During my student days when there were no known vitamins, rickets did not assume such dread significance, and it is only recently that we find the term on the lips of every physician and layman. Is it possible that in the background lies the propaganda of interested industries? Or is there really an increase in the incidence of the disease?

I am not going to review the subject this morning in the classical style of conventional etiology, pathology and symptomatology. You are familiar with the present-day tendencies. One must penetrate deep into the wilderness indeed to escape the blaring radio and the bombardment of leaflets extolling the virtues of vitamin D as it exists in cod liver oil, halibut liver oil, salmon liver oil, irradiated ergosterol (*i. e.*, viosterol), milk of cows receiving irradiated yeast in their fodder, and irradiated milk. I will not even discuss the recent findings of Bills of the Mead Johnson Company describing differences in the vitamin D action of cod liver oil and the oil of the tuna. There is still much scientific work to be done. Today I want to discuss the subject from a purely clinical standpoint with special reference to some of my thoughts and observations during the last five years.

Probably every pediatrician has noted that some babies develop signs of rickets in spite of receiving supposedly adequate amounts of vitamin D. These findings are usually ignored and the parents assured that the baby is perfect. I have seen little reference to this phase of the subject in scientific literature. One hears more of it in the "off the record" conversations at the medical meetings.

In view of the tradition that rickets becomes most apparent during periods of rapid growth, I have often asked myself whether the present-day craze for huge babies may not be a hitherto unsuspected factor. In this category does a factor lie in the concentrated high caloric diets now so generally used which may induce a period of unnatural growth? Is it also possible that cod liver oil which on the one hand contains the antirachitic vitamin but on the other increases the size of the subject has a disadvantageous as well as an advantageous effect?

There is also another possibility which for some reason or other has been overlooked by pediatricians, namely the effect of the reaction of the intestine. This latter is the specific study I have been making during the last years and is the one I am going to report today.

In previous publications concerned with infant nutrition we have reported that the addition of 12 per cent lactose to boiled whole cow's milk is generally followed both by an increase in the hydrogen ion concentration and the gram-positive flora of the stool. In other words, there is in some respects a trend toward the stool of the breast-fed. Other sugars studied failed to give similar results. But on the other hand, babies receiving such concentrated high caloric mixtures developed nutritional disturbance presumably from overfeeding.

In 1926 Bergeim reported experiments in albino rats showing a better absorption of calcium when given with lactose than with other carbohydrates. This he attributed to the increase in intestinal acidity following the use of lactose.

During recent year lactic acid milk and other concentrated foods have shown increasing popularity. The addition of acid to cow's milk unquestionably facilitates gastric digestion, but we have shown that the stool remains alkaline. During these years lactose has been practically discarded in infant feeding. Is it possible that the feedings so generally employed fail to acidify the intestine sufficiently to promote proper calcium absorption and in themselves create an increased demand for antirachitics? Can there be an increased incidence of rickets due not only to the caloric content but also to the chemical nature of the formulae used?

In an effort to solve one phase of this problem we have contrasted the effect of a maltose-dextrin preparation with that of lactose upon the development of rickets when the respective carbohydrates were added in equal quantities to diluted cow's milk. The study has been both clinical and metabolic. The present report concerns the clinical observations on 20 infants.

**Method.**—The infants were admitted to the hospital as soon as possible after birth and kept in a separate room with special nursing care. No vitamin D was given in any known form. Feedings consisted of ordinary certified milk with no vitamin D addition, diluted with distilled water and boiled one minute. The carbohydrates used were a maltose-dextrin

preparation, lactose and beta-lactose. As our previous work had been done with mixtures of whole cow's milk with 12 per cent carbohydrate addition, it was first planned to use such a mixture, but in quantities restricted to the caloric needs of the infants. As will be seen, the results in the first two infants precluded further use of this combination. So that mixture was diluted to one half or two thirds strength as indicated by the patient's age. In such dilution the relation of carbohydrate to protein remained unchanged.

Calcium and phosphorus intake and excretion were determined in the usual type of metabolic experiment. These results will be reported in a subsequent publication.

Clinical observations consisted of monthly physical and roentgenological examinations as well as determinations of blood calcium and phosphorus.

These clinical observations were presented at a recent meeting of the Chicago Pediatric Society\* and I will now give them informally.

**Results.**—The chart (Fig. 158) shows the babies studied with reference to the calendar and the diet. Unfortunately for scientific work we had to take the babies when we could get them. Babies 1 and 2 are the only ones receiving the original mixture of whole milk with 12 per cent carbohydrate addition, one lactose, the other maltose-dextrin. All the others received dilutions of the above mixture with the exception of babies 17 and 18, who received whole cow's milk with no addition during most of the period, and babies 10 and 13 who received breast milk.

In this chart we have graded each baby, considering 10 as perfect. The grades were reached by considering physical, roentgenological and blood chemical examinations as well as the reports and impressions of impartial nurses and house physicians in charge of the infants. It will be seen that in this series the babies on lactose showed a very slight superiority. However, it must be remembered that only 20 babies were studied. Observations were extended over four years

\* December 18, 1934.

and conditions and seasons were not comparable. Also the rating was to a considerable extent subjective. Conclusions should not be definite until the chemical analyses are completed.

While there may have been a slight clinical difference between the babies receiving lactose and those on maltose-dextrin, the striking finding was the low incidence of any appreciable

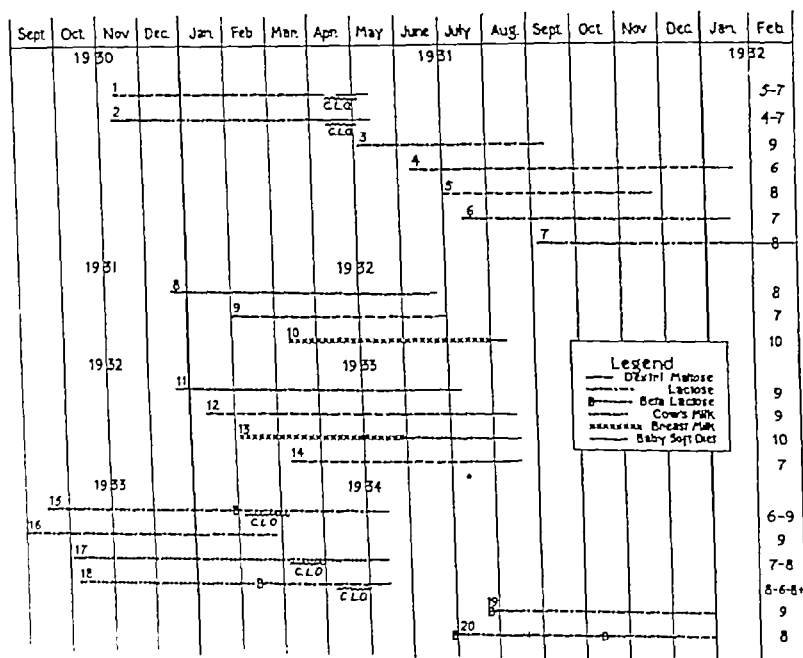


Fig. 158.—The cases grouped according to the length of time under observation, the calendar and the diet prescribed.

degree of rickets in either group. Far more important than differences in the type of carbohydrate used was the difference shown between infants receiving cow's milk with high carbohydrate, cow's milk with no addition and cow's milk diluted and with carbohydrate addition. While under no circumstances questioning the importance of vitamin D, one feels that in these findings there is a suggestion of a dietetic element not as yet clearly defined.



The chart (Fig. 159) shows the findings in baby 13, who received breast milk and served as a control; in babies 17 and 18 who received whole cow's milk and in babies 1 and 2 who received whole cow's milk with 12 per cent carbohydrate. The chart shows the clinical findings as well as the results of monthly x-ray and blood chemical examinations.

The contrast in the findings is startling. It is only fair to state that babies 1 and 2 were twins, came to us somewhat

Baby's No	1st Month	2nd	3rd	4th	5th	6th	7th	8th
13	Ca 122 Cr? P 56 XR-0	Ca 111 P 51 XR-0	Ca 113 P 63 XR-0	Ca 96 P 59 XR-0	Ca 117 P 64 XR-0	Ca 98 P 59 XR-0	Ca 11 Ry? P 58 HG XR-0	
17	Ca 11 P 52 XR-0	Ca 103 Ry? P 57 HG? XR?	Ca 104 Cr? P 47 Ry? XR? HG?	Ca 105 Ry? P 50 HG? XR?	Ca 108 Ry? P 61 HG? XR?	Ca 103 Cr? P 53 Ry? XR? HG?	Ca 108 Cr? P 50 Ry? XR? HG?	
18		Ca 107 P 64 XR-0	Ca 113 Ry? P 59 HG? XR?	Ca 109 Cr? P 55 Ry? XR? HG?	Ca 92 Ry? P 60 HG? XR?	Ca 91 Ry? P 63 HG? XR?	Ca 97 Cr? P 50 Ry? XR? HG?	Ca 115 Cr? P 53 Ry? XR? HG?
1	Cr?	Ca 110 Cr? P 32 Ry?	Ca 62 Cr? P 55 Ry? XR+	Ca 88 Cr? P 46 Ry? HG+	Ca 81 Ry? P 45 Ca 84 XR+ P 36	Ca 76 Ry? P 32 HG? XR+	Ca 101 Ry? P 61 HG? XR+	Legend Cr = Craniotabes Ry = Rosary HG = Hamson's Groove XR = X-ray ? = Milk * = Family Diet M = Whole Cows M.R. BL = Beta Lactose
2	Ry?	Ca 94 Cr? P 29 Ry? HG?	Ca 71 Cr? P 49 Ry? XR+ HG+	Ca 72 Cr? P 45 Ry? XR+ HG+	Ca 76 Ry? P 31 HG? XR+ Ca 86 P 36	Ca 89 Cr? P 36 Ry? XR+ HG+	Ca 96 Ry? P 63 HG? XR+	

Fig. 159.—The blood calcium and phosphorus as well as the x-ray findings and the presence of craniotabes and rosary on diets of breast milk, whole cow's milk, and whole cow's milk with 12 per cent carbohydrate.

later than the other infants, and were slightly rachitic upon admission. All these factors probably played a part in determining the severity of the rickets which was by far more pronounced than in any of the babies studied. But at any rate there was no spontaneous improvement in the condition. We did not feel justified in repeating the experiment though at the conclusion of the period of observation a brief treatment

with cod liver oil brought the findings rapidly to normal. The contrast between these two babies and the breast-fed is certainly striking. The two babies receiving whole cow's milk, while not showing such distinctive blood and x-ray findings, averaged between the two groups on clinical examination.

The chart (Fig. 160) contrasts babies 8 and 9 and 11 and 12, two receiving lactose mixtures and two maltose-dextrin. The findings here are typical of the majority of the infants. To

Baby's No	1st Month	2nd	3rd	4th	5th	6th	7th	8th
8		Ca10.4 P 6.2 XR-0	Ca10.5 P 7.3 Ry? XR-0	Ca10.2 P 7.8 Ry? XR-0	Ca11.3 P 7.5 Ry? XR-0	Ca 9.3 Cr? P 5.1 Ry? XR-0 HG?	Ca10.5 P 7.2 Ry? XR-0 HG?	
		M+6%L		M+6%L		M+6%L		
9		Ca13.0 Cr? P 7.2 Ry? XR-0	Ca10.5 P 7.8 Ry? XR?	Ca11.4 P 7.5 Ry? XR?	Ca10.8 P 5.9 Ry? XR? HG?	Ca10.6 P 6.7 Ry? XR? HG?		
		M+6%L		M+6%L		M+6%L		
11		Ca10.8 Cr? P 5.5 XP ?	Ca11.1 P 6.4 XR-0	Ca10.8 P 5.5 XR-0	Ca 9.6 Cr? P 6.2 Ry? XR-0 HG?	Ca10.0 Cr? P 4.9 Ry? XR-0 HG?	Ca10.6 P 5.5 Ry? XR-0 HG?	
		M+6%L		M+6%L		M+6%L		
12	Ca11.6 Cr? P 7.5 XR-0	Ca10.9 P 5.6 XR-0	Ca10.8 P 6.0 XR?	Ca10.9 P 5.4 Ry? XR?	Ca10.2 Cr? P 4.9 Ry? XR? HG?			
	M+6%L		M+6%L		M+6%L		M+6%L	

Legend	
Cr	Crematobes
Ry	Rosary
HG	Harrison's Groove
XR	X-Ray
?	Mild
M	Milk
L	Lactose

Fig. 160.—Same as Fig. 159 on diets of milk with either maltose-dextrin or lactose addition.

our great surprise most of the infants went through the six months' observation period with little abnormality on x-ray examination and with normal blood chemistry and phosphorus. Physical examination apparently proved a more delicate diagnostic index than laboratory findings, for most of the infants at some time showed a mild rosary or Harrison's groove. But these findings were scarcely more marked than in some infants who had received routine treatment with cod liver oil. Again during the observations a mild rosary and Harrison's groove

might appear for a time and then improve spontaneously. Certainly not all the improvement seen in clinics and private practice during the first six months can be attributed to antirachitic prophylactics and remedies. Craniotabes proved perplexing. It occurred in some degree in all the infants during the early weeks. Then it disappeared. However, in the few babies developing true rachitic findings during and after the fifth month it reappeared. Apparently it is of no significance until this later period.

Baby's No	1st Month	2nd	3rd	4th	5th	6th	7th	8th			
15	Ca109 P 60 XR-0		Ca106 P 60 XR?	Cr? Ca10 HG? P 51 Ry?	Ca 98 Cr+ P 46 Ry+ XR+ HG+?	Ca 90 Cr+? P 39 Ry+ XR+ HG+	Ca109 Ry? XR? HG?	Cr? Ca105 Ry? HG? Ca119 P58 XR0			
	<div>12/17+5%L</div> <div>13/17+8%L</div> <div>14/17+10%L</div> <div>15/17+12%L</div>										
19	Ca125 P 42 XR-0	Ca112 P 58 XR-0	Ca116 P 66 Ry? XR-0 HG?	Ca104 P 63 XR-0	Ca100 P 61 Ry?	<div><div>Legend</div><div>Cr = Craniotabes</div><div>Ry = Rosary</div><div>HG = Harrison's Groove</div><div>XR = X-Ray</div><div>? = Mild</div><div>+? = Family Definite</div><div>M = Whole Cow's Milk</div><div>BL = Beta Lactose</div></div>					
	<div>12/17+6%BL</div> <div>13/17+8%BL</div>										
20	Ca118 Cr? P109 XR-0	Ca109 P 55 XR-0			Ry+?	Ry+?					
	<div>12/17+5%BL</div> <div>13/17+8%BL</div> <div>14/17+10%BL</div>										

Fig. 161.—Same as Fig. 160 on diets of milk with the addition of beta-lactose.

The chart (Fig. 161) contrasts babies 19 and 20. They were both started on a milk mixture with beta-lactose addition, but later baby 20 received maltose-dextrin for some months. Here again the findings are similar to those in the preceding chart. Baby 15 is also shown in this chart, illustrating the effect of cod liver oil. This infant was started on a mixture of two thirds milk with low carbohydrate. He was the only infant on any milk dilution to develop pronounced clinical

symptoms. Here the striking influence of cod liver oil is shown. But what is even more surprising is the relatively small amount of the oil necessary. From the middle of February 2 teaspoonfuls were given daily. By March the laboratory and clinical signs showed decided improvement. By April the baby had two teeth. In this infant, simultaneously with the giving of the oil, a gram-negative flora changed to gram-positive and was so maintained after the oil was discontinued.

Average Caloric Consumption Per Pound Body Weight.																				
Baby No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Wt. at birth	WCH	WCH	%L	%DM	%DM	%L	%L	%DM	B-M	%L	%DM	%L	%DM	%DM	%L	%L	WCH	WCH	%BL	%BL
2	12	20	2%	60		50	38	44	59		48	60		56	55					51
4				54		40	48	57	61		48	54		64	57					59
6				52		48	42	55	60	70	63	60	56		59	57	62	69	49	58
8	63	53	70		51		50	48	60	63	63	64	58	60	66	58	65	66	49	57
10	55	50	47	55	51	62	55	46	60	59	54	76	55	59	50	68	66	67	65	61
12	57	50	47	55	51	62	55	46	60	59	54	76	55	59	50	68	66	67	65	61
14	60	53	56	50	60	60	47	57	50	83	52	64	51	63	69	63	62	49	60	
16	58	62	61	46	59	34	50	60	54	51	78	55	38	56	60	69	60	58	45	56
18	53	66	57	44	50	53	51	50	56	50	45	82	54	55	55	59	45	56	46	52
20	48	59	55	48	51	52	48	54	46	44	77	54	44	52	55	55	56	58	46	50
22	50	53	53	42	50	54	50	54	49	46	77	52	55	50	55	55	53	54	45	48
24	48	58	49	49	45	50	53		47		67	51	49	49	53	51	55	44	46	
26	54		49	50	51	52	50		42		65	50		51	53	51	63		40	
28			56	47	51						62	53		50	54	51				
30				45											55		52			
32															55					
34															55					

B-M = Breast Milk  
 C.L.O. = Cod Liver Oil  
 W.C.M. = Whole Cow's Milk  
 %L BL or DM = % Milk + 6% Lactose, Beta Lactose or Dextrose-Maltose  
 %L BL or DM = % Milk + 6% Lactose, Beta Lactose or Dextrose-Maltose

† Sick  
 ‡ Detritus  
 † Sick

Fig. 162.

In other attempts we were not able to obtain the same effect of the oil upon the flora.

**Height and Weight.**—All of the babies studied were definitely below the standards given as normal in the accepted tables. Even those who were roentgenologically and chemically nonrachitic and who seemed in perfect nutritional condition weighed as much as 2 pounds below the accepted average. Here, as in the infant just demonstrated, one is uncer-

tain whether the finding is due to "hospitalism" or to the lack of cod liver oil. If cod liver oil has the faculty of hanging several apparently unnecessary pounds on a normal infant, it may have an injurious as well as a beneficial effect.

*Caloric Intake.*—The table (Fig. 162) shows the average caloric intake of each baby over periods of two weeks each. The table affords a comparison between the energy consumption of the majority of infants who showed very mild clinical rickets and those few showing no signs at all. It also shows the effect upon the caloric intake of increasing the concentration of the diet.

During the first few weeks the findings can be disregarded due to adjustments of the diet. Looking at the table as a whole, one sees at first no consistency in the findings. Or at any rate, there is no correlation in any one infant between the severity of the signs and the caloric intake. On the other hand, we have as controls baby 10 who was a perfect example of the breast-fed and baby 19 who was the most perfect clinically of the artificially fed. In these babies the caloric intake was not only decidedly less than in the others, but also showed a gradual reduction during each succeeding period. On the other hand, baby 11 who was practically normal clinically took a high amount. This baby was very small and seemed to require the amount given even for slight gain. He remained the smallest of the group at the time of his discharge from the hospital. Again baby 13, a breast-fed infant, took a surprisingly high diet. He was definitely below normal nutritionally and suffered for a time from generalized furunculosis. While it is difficult to formulate definite conclusions, one gets a certain clinical impression that the rachitic infants generally consumed more calories than were necessary for a normal gain in weight; or at any rate, they continued a high caloric consumption over a longer period of time with no spontaneous reduction in intake as did babies 10 and 19. For instance, baby 20 showed definitely more positive findings than did baby 19. The difference in caloric intake is apparent.

I always had the impression that babies on concentrated

diets automatically restricted their caloric intake to their requirements. This is definitely not so. Babies 1 and 2 on the most concentrated diet were frequently hungry and dissatisfied with the quantities offered. It will be seen in every case that when the diet was concentrated to higher caloric value, the infant invariably increased his caloric intake to a quantity greater than was necessary for a gain in weight. He did not adjust his food intake to his caloric need. In other words, concentrated diets lead to overfeeding. This may be of importance in the long continued usage of such formulae.

**Relations of the Elements of the Diet.**—Rickets developed in decreasing severity in diets as follows:

Whole cow's milk with 12 per cent carbohydrate.

Whole cow's milk.

Whole cow's milk with 12 per cent carbohydrate appropriately diluted.

Breast milk.

The milk mixtures uniformly used showed a relation of carbohydrate to protein approximating that in human milk. With the exception of those in which overfeeding played a rôle, these formulae even in the absence of vitamin D were accompanied by rickets of only a mild type. These observations should be repeated with other formulae. Possibly the proportions of the mixtures may have been of some importance.

**Growth Curves.**—The chart (Fig. 163) shows the weight curves of four infants. One received cow's milk with 12 per cent carbohydrate; the second, a dilution of the above; the third, cow's milk with no addition, and the fourth, breast milk. Here again we see another manifestation of the different effects of these formulae. All these babies were subjected to monthly determinations of blood calcium and phosphorus as well as to repeated periods on the metabolism bed. In spite of these interruptions the breast fed infant pursued a relatively smooth and consistent course. The baby receiving the milk dilution was next. The baby on undiluted cow's milk fell below the standards of the others while the one receiving the high caloric mixture had a turbulent time. The

latter curve is also interesting in that it shows that a high caloric diet does not necessarily lead eventually to a large baby. While the growth of this infant was first rapid and far above normal, the curve eventually flattened out to approach the others at about the six-month period. Excessive feeding then could not obviate nature's plan for the eventual weight of this infant and he had to dispose of his extra food as best he could.

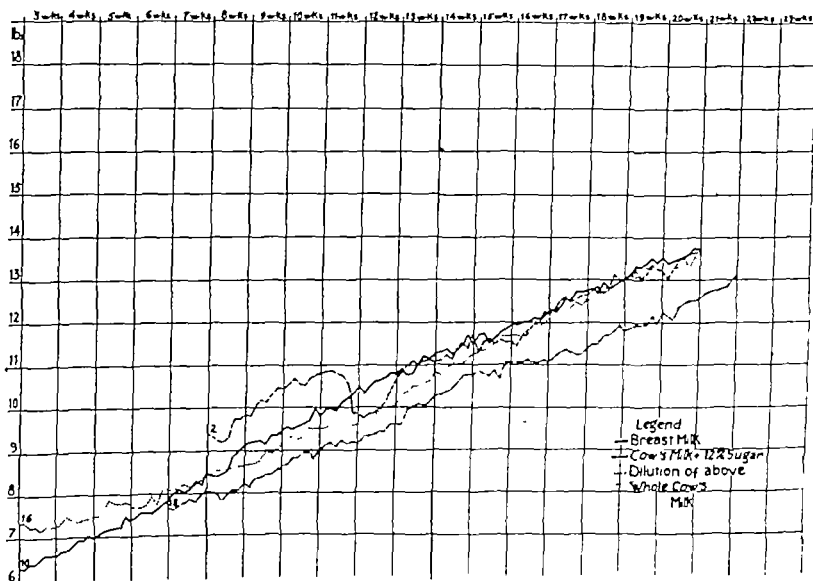


Fig. 163.—The weight curves on diets of breast milk, cow's milk with 12 per cent carbohydrate, dilutions of the latter, and undiluted whole cow's milk.

If there is a dietetic factor in the prevention of rickets it probably is in the combination of proper calories and proper proportion of food elements existing in ideal form in human milk.

**Cod Liver Oil.**—The fact that most of the infants went through six months in a hospital with no cod liver oil, no known source of vitamin D or ultraviolet light, and with rachitic findings of only a very mild type cannot be overlooked. Again the relatively small amount of cod liver oil

necessary to right the condition raises two questions. Is the effectiveness of the oil influenced by physicochemical conditions in the intestine? In baby 15 (Fig. 161) the laboratory and clinical response to relatively small amounts of the oil was striking. Or is it true that cod liver oil and vitamin D are prescribed in unnecessary quantities and that we physicians and our patients are being exploited?

Medical men have undoubtedly known that many babies will not develop rickets during the first six months, even if given no antirachitic. They have undoubtedly suspected that antirachitics may be given in unnecessary quantities and they have probably suspected that determinations of blood calcium and phosphorus as well as  $\alpha$ -ray examinations are not reliable indices as to the existence of rickets. But for some reason or other the whole subject has been shrouded in more or less silence.

**Summary.**—To summarize this clinic, we have specifically raised the question as to why some babies develop signs of rickets in spite of a supposedly adequate dosage of vitamin D. We have suggested that one factor might lie in the present-day methods of feeding which seem to us to lay undue emphasis upon the desirability of maximal size values.

We have also raised the question and entered into a scientific study of the importance of the chemical effect upon the infant's intestine of some of the diets commonly used. If calcium and phosphorus are absorbed more readily from an acid intestine, an increased incidence of rickets might be ascribed to present-day methods of feeding because most of the popular formulae do not lead to high intestinal acidity. The only carbohydrates which seem to do this are lactose and beta-lactose and up to recently these have not been used extensively.

In the 20 babies studied clinically with special reference to the development of rickets, there seemed little difference between those receiving maltose-dextrin and those receiving lactose. Those on lactose and beta-lactose may have shown slight clinical superiority but such conclusion is tentative until further chemical studies are completed.



Much more apparent were the differences shown by babies receiving whole boiled cow's milk with 12 per cent carbohydrate addition, dilutions of this mixture, whole boiled cow's milk with no carbohydrate addition and breast milk. As none of these babies received antirachitics, it is presumable that a dietetic factor was also involved. Excluding the influence of the degree of acidity of the intestinal contents, this dietetic factor probably lies in the caloric content, concentration, nature and percentages of the food elements in the formula. Certainly in those few infants developing signs of rickets the severity of the condition in a general way paralleled the concentration of cow's milk and the excess of carbohydrate in the formula.

In this study a number of incidental observations were of interest.

It was somewhat out of the ordinary to note that most of the babies could spend six months in a hospital ward, receive no antirachitics and show rickets of only the very mildest type or often no rickets at all. In the babies with positive signs, cod liver oil was effective in smaller doses and over a shorter period of time than I had thought necessary.

In this study physical examination proved a far more delicate method of determining the early development of rickets than did the x-ray or determinations of blood calcium and phosphorus. Craniotabes was of little diagnostic significance before the fourth or fifth month.

# CUMULATIVE INDEX

- ABDOMINAL distention in pneumonia, treatment, *July*, 13  
 Hodgkin's disease, *Sept.*, 423-427  
 pain, clinical significance and relief, *Jan.*, 1113-1129  
     severe, following emotional storm, *Sept.*, 399-402  
     trauma, psychic effect, *Nov.*, 837-845  
 Abortion, habitual, *Nov.*, 829  
 Abscess, Bezold's, *Jan.*, 1045  
     of Bartholin's gland in gonorrhea, *Nov.*, 919  
     of brain, eye symptoms, *Jan.*, 1214  
     of lung, bronchial obstruction in, *Sept.*, 456, 462  
     complicating pneumonia, *July*, 33, 34  
     parapharyngeal, *Jan.*, 1152  
     pelvic, gonorrheal, *Nov.*, 921  
     subperichondrial, *Jan.*, 1051  
     suburethral, gonorrheal, *Nov.*, 922  
 Acetyl-B-methylcholin in paroxysmal tachycardia, *Nov.*, 860  
 Achlorhydria in conditions other than pernicious anemia, *July*, 48  
 Achlorhydric anemia, simple, *July*, 69  
 Acidosis, diabetic, in children, prevention, *July*, 279  
 Acrodynia, *Nov.*, 957  
 Acromegaly, *Nov.*, 822-824  
 Addison's disease, diagnosis and treatment, *Sept.*, 383-398  
     salt therapy, *Nov.*, 959-965  
 Addisonian anemia. See *Anemia, pernicious.*  
 Adiposogenital dystrophy, *Nov.*, 826-830  
 Agranulocytic angina, *July*, 103-122  
 Air embolism in artificial pneumothorax, *Nov.*, 908  
 Albuminuric retinitis, *Jan.*, 1236  
 Alcohol in production of pellagra, *July*, 60  
     of sprue, *July*, 63  
     injections, intraspinal, for pelvic pain, *Jan.*, 1133  
     in glossopharyngeal neuralgia, *Jan.*, 1029  
     in occipital neuralgia, *Jan.*, 1030  
     in superior laryngeal neuralgia, *Jan.*, 1029  
     in trigeminal neuralgia, *Jan.*, 1018-1027  
 Alcohol, use of, in angina pectoris, *Nov.*, 884; *Jan.*, 1104  
 Alcoholic neuritis, *July*, 68; *Nov.*, 951  
 Alcoholism, acute, convulsions in, *July*, 244  
 Alopecia areata, *Jan.*, 1242  
 Amidopyrine in causation of agranulocytic angina, *July*, 110-118  
 Amputation of cervix in gonorrhea, *Nov.*, 917  
 Amyl nitrite in angina pectoris, *Jan.*, 1099  
 Amyloid nephrosis, proteosuria in, *July*, 177-184  
 Amyloidosis, Congo red test, *July*, 179  
 Anastomosis, intestinal, multiple, macrocytic anemia following, *July*, 67  
 Anemia, achlorhydric, simple, *July*, 69  
     addisonian. See *Anemia, pernicious.*  
     after gastrectomy and gastro-enterostomy, *July*, 67  
     deficiency, *July*, 37  
     Dibothriocephalus latus, *July*, 64, 65  
     hypochromic, idiopathic, *July*, 69, 72  
     in inoperable cancer, treatment, *July*, 201  
     macrocytic, *July*, 38  
         in association with mechanical defects in gastro-intestinal tract, *July*, 67  
         tropical, *July*, 66  
     microcytic, *July*, 59, 69  
     nutritional, *July*, 37-77  
     of pregnancy, *July*, 39, 65  
     pernicious, *July*, 37-59  
         as deficiency disease, *Sept.*, 469  
         comparison with pernicious leukopenia, *July*, 105  
         neurological manifestations and their treatment, *July*, 79-89  
         secondary, classification, *July*, 91  
         treatment, *July*, 91-101  
 Angina, agranulocytic, *July*, 103-122  
     pectoris in gallbladder disease, *Nov.*, 654  
     pain simulating, *Jan.*, 1077-1083  
     treatment, *Nov.*, 880-887; *Jan.*, 1085-1111  
 Anorexia in inoperable cancer, treatment, *July*, 197  
 Antophysin, *Nov.*, 818

- Antuitrin, *Nov.*, 818  
 Aorta and its larger branches, embolism and thrombosis of, *July*, 159-170  
 Aortic stenosis, calcareous, clinical and roentgenologic comments, *Sept.*, 487-497  
 Appendicitis, acute, atypical, diagnosis, *July*, 185-194  
   pain in, *Jan.*, 1122, 1124  
 Apple diet in diarrhea of infants and children, *July*, 301-305  
 Arm, epitheliomas of, simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610  
 Arrhythmia in gallbladder disease, *Nov.*, 658  
 Arsenic in treatment of secondary anemias, *July*, 99  
 Arsenical neuritis, *Nov.*, 955  
 Arterial hypotension, *Nov.*, 865-871  
 Arteriosclerosis associated with hypertension, *July*, 139  
   eye symptoms, *Jan.*, 1209  
 Arteriosclerotic retinitis, *Jan.*, 1210  
 Arteriovenous fistula, congenital, *Sept.*, 525-533  
 Arthritis, chronic infectious, fever therapy in, *Sept.*, 590  
   inactivation by jaundice, *Sept.*, 573-583  
   relief by cholecystostomy and cholecystectomy, *Nov.*, 697  
   gonorrheal, fever therapy, *Sept.*, 551-559, 589  
   menopausal, *July*, 218  
   of feet, pain in, *Jan.*, 1071  
   postoperative, acute, identification of, *Sept.*, 560-566  
   prevention and treatment, *Sept.*, 566-573  
 Arthrodesis for sciatic pain, *Jan.*, 1038  
 Ascorbic acid, *Sept.*, 482  
 Asthma, fever therapy, *Sept.*, 591  
   simulating tracheal and bronchial obstruction, *Sept.*, 453  
 Atelectasis, massive, *Sept.*, 457  
 Auricle of ear, pain in, relief, *Jan.*, 1050-1054  
 Auricular fibrillation, *Sept.*, 511-515  
 Autohemotherapy in pruritus, *Nov.*, 982  
 Autovaccination, *Jan.*, 1280
- BACILLUS diphtheriae, rapid culture method, *Nov.*, 736  
 Backache, relief of, *Jan.*, 1033-1038  
 Bartholin's gland, gonorrheal abscess, *Nov.*, 919  
 Basedow's disease, eye symptoms, *Jan.*, 1204
- Basophilism, pituitary, *Nov.*, 831  
 Bed-wetting, *July*, 287  
 Beri-beri, *July*, 68  
   in gastro-intestinal disease or abnormality, *Sept.*, 468, 469  
   vitamin deficiency in, *Sept.*, 481  
 Bezold's abscess, *Jan.*, 1045  
 Bile, laboratory study, *Nov.*, 680-684  
   pigment in secondary anemias, *July*, 100  
 Biliary calculi. See *Cholelithiasis*.  
   colic, *Nov.*, 642; *Jan.*, 1118, 1124  
   disease following cholecystectomy for stones, *Nov.*, 689  
   drainage, nonsurgical, *Nov.*, 677-688  
   dyskinesia, *Nov.*, 669, 673  
 Birth injuries, cerebral, convulsions due to, *July*, 249, 254  
   corrective motor education in, *Nov.*, 807-815  
 Black dot of scalp, *Jan.*, 1248  
   tongue, *July*, 59  
 Bladder neck masses, gonorrheal, *Nov.*, 924  
 Blastomycosis, cutaneous tuberculosis simulating, *Sept.*, 613, 617  
 Blindness, night, in gastro-intestinal disease or abnormality, *Sept.*, 468, 469  
 Blood, cholesterol determinations, *Jan.*, 1167  
   clotting function, diets to increase and decrease, *Nov.*, 989-999  
   dyscrasia, atypical, four clinical types of jaundice arising from, *Sept.*, 545-550  
 Bone, giant-cell tumor, roentgen treatment, *Sept.*, 601  
 Brain, abscess of, eye symptoms, *Jan.*, 1214  
   defects, congenital, convulsions due to, *July*, 251, 254  
   tumors, eye symptoms, *Jan.*, 1217  
   gastro-intestinal manifestations, *Jan.*, 1260  
   headache in, *Jan.*, 1203  
   pain about oral cavity in, *Jan.*, 1065  
 Breath, uremic, *July*, 237  
 Brodie's serum in poliomyelitis prophylaxis, *Nov.*, 742  
 Bronchiectasis, abdominal pain in, *Jan.*, 1116  
   treatment, *Jan.*, 1171  
 Bronchopneumonia, tuberculous, in children, *Nov.*, 717, 718  
 Bronchus, obstruction of, clinical manifestations, with bronchoscopic observation, *Sept.*, 453-462  
 Burning tongue, *Jan.*, 1065

- CALCAREOUS aortic stenosis, *Sept.*, 487-497
- Calcium bilirubin masses in bile, *Nov.*, 681
- Calculus, biliary. See *Cholelithiasis*.
- Carbon monoxide polyneuritis, *Nov.*, 958
- Carcinoma, inoperable, treatment, *July*, 195-204
- multiple, complicating chronic ulcerative colitis, *Sept.*, 408-410
- of bronchus causing obstruction, *Sept.*, 455
- of cervical stump after hysterectomy, *Sept.*, 352
- of cervix, incidence, *Sept.*, 350
- pain in, relief, *Jan.*, 1133
- of colon, cooperative management, *Sept.*, 619, 621, 625
- of kidney, roentgen treatment, *Sept.*, 601
- of lungs, bronchial obstruction in, *Sept.*, 456
- of skin, roentgen treatment, *Sept.*, 599
- of small intestine, *Sept.*, 366
- of thyroid gland, roentgen treatment, *Sept.*, 600
- roentgen therapy, *Sept.*, 598-603
- Cardiospasm in gallbladder disease, *Nov.*, 653
- Carotene, *Sept.*, 479
- Caruncle, urethral, *Nov.*, 923
- Cataract, diabetic, *Jan.*, 1232
- Catarrhal jaundice, biliary drainage in, therapeutic value, *Nov.*, 685
- Cauterization of cervix for cervicitis, *Sept.*, 354
- in gonorrhea, *Nov.*, 915, 918
- Cerebral accidents, coma of, treatment, *Jan.*, 1270
- birth injuries, convulsions due to, *July*, 249, 254
- corrective motor education in, *Nov.*, 807-815
- Cerumen, impacted, *Jan.*, 1052
- Cervical stump, carcinoma of, following hysterectomy, *Sept.*, 352
- Cervicitis, *Sept.*, 349
- cautery treatment, *Sept.*, 354; *Nov.*, 915, 918
- Elliott heat treatment, *Sept.*, 353
- Cervix uteri, amputation of, in gonorrhea, *Nov.*, 917
- carcinoma of, pain in, relief, *Jan.*, 1133
- gonorrhea of, treatment in nulliparous, *Nov.*, 918
- in parous, *Nov.*, 914
- lesions of, *Sept.*, 347-357
- tetracyanic acid, *Sept.*, 482
- Chickenpox, immunization, *Jan.*, 1290
- Children, diseases of, symposium on, *Nov.*, 701
- Choked disk in brain abscess, *Jan.*, 1215
- in brain tumor, *Jan.*, 1217
- Cholangitis, *Nov.*, 665
- biliary drainage in, therapeutic value, *Nov.*, 687
- Cholecystectomy for stones, biliary disease following, management, *Nov.*, 689
- relief of chronic arthritis by, *Nov.*, 697
- Cholecystitis, chronic, diagnosis, *Nov.*, 641-648
- lenta, *Nov.*, 665
- Cholecystography, *Nov.*, 644
- Cholecystopathica spastica, *Nov.*, 670
- Cholecystostomy, relief of chronic arthritis by, *Nov.*, 697
- Cholelithiasis, cholecystectomy for, biliary disease following, management, *Nov.*, 689
- diagnosis, *Nov.*, 641-648
- Cholesterin crystals in bile, *Nov.*, 681
- Cholesterol in blood, determinations, *Jan.*, 1167
- Chordotomy for pelvic pain, *Jan.*, 1140
- Chorea in children, fever therapy, *Sept.*, 591; *Nov.*, 771-784
- Choreo-athetosis, *Nov.*, 808, 809
- Chvostek's sign in tetany, *July*, 242, 255
- Cinchophen in acute postoperative gout, *Sept.*, 570
- Climacteric. See *Menopause*.
- Clotting function of blood, diets to increase and decrease, *Nov.*, 989-999
- Cold test in hypertension, *Sept.*, 518
- Colds, common, in infants and children, *Nov.*, 745-750
- Colic, biliary, *Nov.*, 642; *Jan.*, 1118, 1124
- renal, *Jan.*, 1119, 1124
- Colitis, mucous, *Jan.*, 1123, 1128
- ulcerative, chronic, management, *Sept.*, 403-407
- two carcinomas complicating, *Sept.*, 408-410
- regional, *Sept.*, 411-422
- Colon, carcinoma of, cooperative management, *Sept.*, 619, 621, 625
- irritable, pain in, *Jan.*, 1123, 1127
- secretory, motor and sensory disturbances in gallbladder disease, *Nov.*, 662, 663
- Coma, diabetic. See *Diabetic coma*.
- treatment, *Jan.*, 1265-1271

- Communicable diseases, recent developments, *Nov.*, 731-744; *Jan.*, 1277-1290
- Complement fixation test in tuberculosis in children, *Nov.*, 724
- Congenital arteriovenous fistula, *Sept.*, 525-533
- brain defects, convulsions due to, *July*, 251
- Congo red test in amyloidosis, *July*, 179
- Conization in gonorrhea of cervix, *Nov.*, 914
- Convulsions, *July*, 233-246
- epileptic, *July*, 259-264
- epileptiform, *July*, 260
- in children, diagnosis and treatment, *July*, 247-265
- jacksonian, *July*, 260
- Copper in treatment of secondary anemias, *July*, 99
- Corns, *Jan.*, 1072
- Coronary disease, pain simulating, *Jan.*, 1077-1083
- occlusion, abdominal pain in, *Jan.*, 1116
- acute, *Sept.*, 499-510
- seasonal incidence in Philadelphia, *July*, 151-157
- thrombosis, angina pectoris and, differentiation, *Jan.*, 1085
- treatment, *Nov.*, 873-880, 887
- Cortical hormone therapy in Addison's disease, *Sept.*, 392-396
- Culture medium, Löwenstein's, in tuberculosis, *Nov.*, 722
- Cutaneous. See *Skin*.
- Cysts, nabothian, *Sept.*, 349
- tubal, in female gonorrhea, *Nov.*, 920
- DALRYMPLE'S sign, *Jan.*, 1208
- Deficiency anemias, *July*, 37
- diseases, methods of production, *Sept.*, 468
- occurrence of, *Sept.*, 466, 474
- Dehydration in inoperable cancer, treatment, *July*, 202
- Delirium in pneumonia, treatment, *July*, 14
- Dental field, pain in, *Jan.*, 1057-1066
- Dermatopolyneuritis, *Nov.*, 957
- Dermatoses, pruritus of, *Nov.*, 979
- Deryl-Hart apparatus, *July*, 31
- Diabetes, eye symptoms, *Jan.*, 1231
- in children, insulin in, *Nov.*, 791-805
- management, *July*, 273-286
- Diabetic coma in children, treatment, *Nov.*, 800
- treatment, *Jan.*, 1268
- Diabetic polyneuritis, *Nov.*, 956
- Diaphragmatic hernia, anginal pain in, *Jan.*, 1083
- pleurisy, abdominal pain in, *Jan.*, 1115
- Diarrhea of infants and children, apple diet in, *July*, 301-305
- Diathermy in gonorrhea of cervix, *Nov.*, 914
- Diathesis, exudative, *July*, 326
- Dibothriocephalus latus anemia, *July*, 64, 65
- Dick test, *Jan.*, 1285
- Diet, apple, in diarrhea of infants and children, *July*, 301-305
- "bleeding" and "clotting," *Nov.*, 989-999
- diabetic, for children, *July*, 274
- in angina pectoris, *Jan.*, 1097
- in coronary thrombosis, *Nov.*, 876, 887
- in pneumonia, *July*, 15, 17
- Karell, *July*, 174
- ketogenic, in epilepsy, *July*, 263
- Dietary treatment of hypertension, *July*, 144
- of inoperable cancer, *July*, 197
- of nephritis with vascular and cardiac complications, *July*, 175
- of secondary anemias, *July*, 97
- Digitalis in nephritis with vascular and cardiac complications, *July*, 174
- Digitalization in pneumonia, *July*, 14
- Diphtheria bacillus, rapid culture method, *Nov.*, 736
- Schick test, *Jan.*, 1282
- toxoid for immunization, *Nov.*, 736; *Jan.*, 1281
- with heart involvement, *Nov.*, 737
- Diphtheritic polyneuritis, *Nov.*, 955
- Diuretics in nephritis with vascular and cardiac complications, *July*, 174
- Diverticula, Meckel's, *Sept.*, 372, 373
- of small intestine, *Sept.*, 372
- Diverticulitis, *Sept.*, 374
- perforation in, management, *Sept.*, 407
- Drugs, convulsant, poisoning in children by, *July*, 256
- in causation of pernicious leukopenia, *July*, 110-118
- poisoning by, treatment, *Jan.*, 1268
- Dwarfism, pituitary, *Nov.*, 825, 826
- Dyscrasia, blood, four clinical types of jaundice arising from, *Sept.*, 545-550
- Dysinsulinism, *July*, 233
- Dyskinesia, biliary, *Nov.*, 669, 673
- Dysmenorrhea, *Jan.*, 1132
- Dyspareunia, *July*, 267, 268

- Dyspepsia in gallbladder disease, *Nov.*, 642
- Dystrophy, adiposogenital, *Nov.*, 826-830
- EAR drops, *Jan.*, 1042  
     drum, blue, *Jan.*, 1048  
     paracentesis of, *Jan.*, 1042  
     rupture of, traumatic, *Jan.*, 1054  
     foreign bodies in, pain due to, *Jan.*, 1052
- Earache, reflex, *Jan.*, 1055  
     treatment, *Jan.*, 1039-1055
- Eclamptic uremia, acute, *July*, 236, 238
- Ectropion of cervix, *Sept.*, 349
- Eczema, contact, *July*, 319-324  
     in infancy and childhood, *July*, 325-331  
     of ear, *Jan.*, 1050
- Edema, stasis, in thrombophlebitis, *Sept.*, 542  
     in varicose veins, *Sept.*, 538
- Elliott heat treatment of cervicitis, *Sept.*, 353
- Embolectomy, *July*, 168
- Embolism, air, in artificial pneumothorax, *Nov.*, 908  
     of aorta and its larger branches, *July*, 159-170  
     pulmonary, simulating coronary disease, *Jan.*, 1079
- Embryoma of testis, *Sept.*, 599
- Emotional storm, severe abdominal pains following, *Sept.*, 399-402
- Empyema complicating pneumonia, surgical management, *July*, 30-33
- Encephalitis, epidemic, eye symptoms, *Jan.*, 1228  
     postvaccinal, *Jan.*, 1280
- Encephalopathy, hypertensive, *July*, 238
- Endocrine therapy. See *Hormone therapy.*
- Enterocolitis, ulcerative, regional, *Sept.*, 411-422
- Enuresis in childhood, causes and treatment, *July*, 287-294
- Epilepsy, idiopathic, *July*, 259-264
- Epileptiform convulsions, *July*, 260
- Epiphyses, separation of, *Nov.*, 830
- Epitheliomas of arm simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610  
     of ear, *Jan.*, 1054
- Epituberculosis, roentgen findings, *Nov.*, 715
- Erb's sign in tetany, *July*, 255
- Erosion of cervix, *Sept.*, 349  
     cautery treatment, *Sept.*, 354
- Erysipelas of auricle, *Jan.*, 1051
- Erythematous lupus, acute disseminated, visceral lesions of, *July*, 333-346
- Erythredema polyneuritis, *Nov.*, 957
- Estrin in menopause, *July*, 220-224
- Evaporated milk for infants, *Nov.*, 787
- Eversion of cervix, *Sept.*, 349
- Ewing's tumor, roentgen therapy, *Sept.*, 602
- Exophthalmic goiter, eye symptoms, *Jan.*, 1204
- Exophthalmos, *Jan.*, 1205
- Extremities, increased length, in arteriovenous fistula, *Sept.*, 526, 528  
     venous diseases, *Sept.*, 535-543
- Exudative diathesis, *July*, 326
- Eyegrounds, examination, *Jan.*, 1198
- Eyes, examination, *Jan.*, 1189  
     in acute disseminated lupus erythematosus, *July*, 337  
     symptoms, diagnostic value in general disease, *Jan.*, 1187-1239
- Eyestrain, headaches due to, *Jan.*, 1202
- FACIAL neuralgia, relief of, *Jan.*, 1017-1028
- Favus of scalp, *Jan.*, 1249
- Febrile diseases in infants, convulsions due to, *July*, 252
- Feeding, infant, difficult cases, *Nov.*, 785-789
- Feet, painful, relief of, *Jan.*, 1067-1075
- Ferments, pancreatic, *Nov.*, 683
- Fever in acute appendicitis, *July*, 193  
     therapy, *Sept.*, 585-595  
     in chorea in children, *Sept.*, 591; *Nov.*, 771-784
- Fibrositis, chronic, inactivation by jaundice, *Sept.*, 573-583
- Fistula, arteriovenous, congenital, *Sept.*, 525  
     gastrojejunal, anemia with, *July*, 67  
     of small intestine, *Sept.*, 377
- Flush, menopausal, *July*, 215
- Follutein, *Nov.*, 818
- Foods, vitamin content, advisability of increasing, *Sept.*, 472
- Foot, march, *Jan.*, 1075  
     strain, *Jan.*, 1073
- Foreign bodies in bronchus causing obstruction, *Sept.*, 457  
     in ear, pain due to, *Jan.*, 1052
- Fractures of ribs, pain in, simulating coronary disease, *Jan.*, 1081  
     of skull, eye symptoms, *Jan.*, 1238
- Fröhlich's syndrome, *Nov.*, 826-830

- Frostbite of ear, *Jan.*, 1053  
Fundus, eye, examination, *Jan.*, 1201  
Fungi in external ear, *Jan.*, 1050  
Furunculosis of ear, *Jan.*, 1049
- GAENSLER's sign in sacro-iliac lesions, *Jan.*, 1036  
Galactose tolerance test, *Jan.*, 1167  
Gallbladder disease, biliary drainage in, diagnostic value, *Nov.*, 679  
therapeutic value, *Nov.*, 687  
diagnosis, *Nov.*, 641-648  
metabolic disturbances in, *Nov.*, 664  
pancreatic disease associated with, *Nov.*, 664  
symposium on, *Nov.*, 639  
symptoms, atypical, *Nov.*, 649-675  
dyskinesia, *Nov.*, 669, 673  
functional disturbances, *Nov.*, 666  
treatment, *Nov.*, 672  
stasis, *Nov.*, 669  
vertigo, *Nov.*, 653  
Gallstones. See *Cholelithiasis*.  
Gas pains, postoperative, *Jan.*, 1125  
Gasserian ganglion, sensory root avulsion, for trigeminal neuralgia, *Jan.*, 1028  
Gastrectomy, anemia following, *July*, 67  
Gastric juice in relation to pernicious anemia, *July*, 41  
lavage for diagnosis of tuberculosis, *Nov.*, 721  
resection for peptic ulcer, recurrences after, *Sept.*, 451  
tetany, *July*, 242  
Gastroduodenostomy, lateral, for peptic ulcer, recurrence after, *Sept.*, 434  
Gastro-enterostomy for peptic ulcer, recurrent and anastomotic ulcer after, *Sept.*, 441  
Gastro-intestinal manifestations of systemic disease and their differential diagnosis, *Jan.*, 1251-1263  
tract in development of deficiency diseases, *Sept.*, 468  
Gastrojejunal ulcer following gastro-enterostomy, *Sept.*, 442  
Gastrojejunal fistula, anemia with, *July*, 67  
Gastrotomy, anemia following, *July*, 67  
Giant-cell tumor of bone, roentgen treatment, *Sept.*, 601  
Giardia intestinalis in bile, *Nov.*, 680  
Gifford's sign, *Jan.*, 1208  
Ginger paralysis, *Nov.*, 953
- Glaucoma, headache in, *Jan.*, 1203  
Glossitis, atrophic, nutritional factors, *July*, 59  
Glossopharyngeal neuralgia, relief of, *Jan.*, 1028  
Goiter, exophthalmic, eye symptoms, *Jan.*, 1204  
Gonadal insufficiencies, pituitary, *Nov.*, 832  
Gonococcal urethritis, fever therapy, *Sept.*, 588  
Gonorrhea in women, *Nov.*, 911-914  
treatment, *Nov.*, 914-926  
Gonorrheal arthritis, fever therapy, *Sept.*, 551-559, 589  
Gout, postoperative, acute, identification of, *Sept.*, 560-566  
prevention and treatment, *Sept.*, 566-573  
Gradenigo's syndrome, *Jan.*, 1046  
Graham test in gallbladder disease, errors in interpretation, *Nov.*, 678  
Grand mal, *July*, 260  
Granulocytoclastic crisis, *July*, 115  
Granulomata of ear, *Jan.*, 1054  
Graves' disease, eye symptoms, *Jan.*, 1204  
Growth in children, nature and rational appraisal of, *July*, 307-317  
Gynecological lesions, pain in, *Jan.*, 1122, 1131
- HALLUX rigidus, *Jan.*, 1074  
Hartmann's solution in diabetic coma, *Nov.*, 803  
Head injuries, eye symptoms, *Jan.*, 1238  
Headache due to migraine, relief of, *Jan.*, 1015  
eyestrain and, *Jan.*, 1202  
in brain tumor, *Jan.*, 1203  
in glaucoma, *Jan.*, 1203  
menopausal, *July*, 217  
pituitary, *Nov.*, 833  
waking, *Jan.*, 1202  
Heart block, convulsions and unconsciousness in, *July*, 243  
frequency, *July*, 123-129  
treatment, *July*, 129-131  
disease, gastro-intestinal manifestations, *Jan.*, 1261  
in pregnancy, management, *Nov.*, 893-899  
failure complicating chronic glomerular nephritis, *July*, 171  
lesions of, in diphtheria, *Nov.*, 737  
Hemolytic crisis, acute, *Sept.*, 548, 549  
jaundice, *Sept.*, 545, 549  
Hemoptysis in pulmonary tuberculosis, management, *Nov.*, 901-904

- Hepatitis, biliary drainage in, therapeutic value, *Nov.*, 687
- Hernia, diaphragmatic, anginal pain in, *Jan.*, 1083
- Herpes zoster of auricle, *Jan.*, 1052
- Hexuronic acid, *Sept.*, 482
- Hilar nodes, tuberculous, *Nov.*, 711
- Hodgkin's disease, abdominal, *Sept.*, 423-427
- itching in, treatment, *Nov.*, 967-970
- Homosexuality, *Nov.*, 938
- Hormone therapy in Addison's disease, *Sept.*, 392-396
- in functional metrorrhagia in young women, *Sept.*, 361
- in menopause, *July*, 220, 221
- in pituitary disorders, *Nov.*, 818
- in secondary anemia, *July*, 100
- Hunt's zoster auricular, *Jan.*, 1052
- Huntton's antibody solution in pneumonia, *July*, 6
- Hydrocephalus, convulsions due to, *July*, 251, 254
- Hydrosalpinx, gonorrheal, *Nov.*, 920
- Hyperinsulinism, *July*, 233
- Hypertension, *July*, 133
- arteriosclerosis with, *July*, 139
- cold test in, *Sept.*, 518
- complicating chronic glomerular nephritis, *July*, 171
- essential, *Sept.*, 517-524
- familial character of, *July*, 137; *Sept.*, 517
- surgical measures for, *Sept.*, 522
- latent, *Sept.*, 521
- malignant, *July*, 134
- menopausal, *July*, 216
- treatment, *July*, 133-149
- Hypertensive encephalopathy, *July*, 238
- Hypertherm, Kettering, *Sept.*, 585
- Hyperthyroidism, gastro-intestinal manifestations, *Jan.*, 1258
- Hyperventilation tetany, *July*, 242
- Hypochromic anemia, idiopathic, *July*, 69
- Hypoglycemia, *July*, 233
- convulsions of, *July*, 234
- Hypogonadism, pituitary, *Nov.*, 828
- Hypoparathyroid tetany, *July*, 242, 243
- Hypotension, *Nov.*, 865-871
- Hysterectomy, carcinoma of cervical stump following, *Sept.*, 352
- Hysteria, traumatic, *Nov.*, 838, 839
- Hysterical convulsions, *July*, 245
- in children, *July*, 260
- JACOBI'S index, *Jan.*, 1166
- Id eruption of scalp, *Jan.*, 1248
- Ileitis, regional, *Sept.*, 413
- Ileum, ulcers of, *Sept.*, 380
- Ileus, *Sept.*, 377
- Illumination tests of eye, *Jan.*, 1195, 1197
- Immunity in newborn, *Nov.*, 733
- Immunization against infectious diseases of childhood, *Nov.*, 731-744; *Jan.*, 1277-1290
- Indigestion, acute, anginal pain in, *Jan.*, 1083
- Infant feeding, difficult cases, *Nov.*, 785-789
- Infantile paralysis. See *Poliomyelitis*.
- Infantilism, pituitary, *Nov.*, 825, 826
- Infections, acute, in infants, convulsions due to, *July*, 251, 252
- resistance to, vitamins and, *Sept.*, 471
- roentgen treatment, *Sept.*, 597
- Infectious diseases of childhood, immunization against, *Nov.*, 731-744; *Jan.*, 1277-1290
- Inflammation of small intestine, *Sept.*, 378
- Inflammatory conditions, roentgen treatment, *Sept.*, 597
- disease, pelvic, gonorrheal, *Nov.*, 920
- Inflations in acute serous otitis media, *Jan.*, 1042
- Influenza meningitis, *Nov.*, 768
- Insomnia in hypertension, treatment, *July*, 144
- menopausal, *July*, 218
- Insulin in diabetes of childhood, *July*, 277; *Nov.*, 791-805
- Intercourse, unsatisfactory, treatment of, *July*, 267
- Intestinal anastomosis, multiple, macrocytic anemia following, *July*, 67
- Intestine, small, lesions of, other than peptic ulcer, *Sept.*, 365-382
- Intussusception, *Sept.*, 378
- Iron therapy in secondary anemias, *July*, 93-96
- Irritable colon, pain in, *Jan.*, 1123, 1127
- Itching, *Nov.*, 971-980
- in Hodgkin's disease, treatment, *Nov.*, 967-970
- treatment, *Nov.*, 980-987
- JACKSONIAN convulsions, *July*, 260
- Jaeger's test types, *Jan.*, 1193
- Jake paralysis, *Nov.*, 953
- Jaundice, catarrhal, biliary drainage in, therapeutic value, *Nov.*, 685
- diagnosis and medical management, *Jan.*, 1163



- Jaundice, four clinical types arising from atypical blood dyscrasia, *Sept.*, 545-550  
 hemolytic, *Sept.*, 545-549  
 in abdominal Hodgkin's disease, *Sept.*, 425  
 in cholelithiasis, *Nov.*, 644  
 inactivation of chronic infectious arthritis and fibrositis by, *Sept.*, 573-583  
 Jejunal ulcer following gastro-enterostomy, *Sept.*, 442  
 Joins, diseases of, *Sept.*, 551-583  
 Juvenile diabetes, *July*, 273-286
- \*KARELL diet, *July*, 174  
 Kerion of scalp, *Jan.*, 1247, 1248  
 Ketogenic diet in epilepsy, *July*, 263  
 Kettering hypertherm, *Sept.*, 585  
 Kidney, carcinoma of, roentgen treatment, *Sept.*, 601  
 disorders, gastro-intestinal manifestations, *Jan.*, 1262  
 in pregnancy, prevention, *July*, 295-299  
 Koerner's syndrome, *Jan.*, 1052  
 Kolmer's serum in poliomyelitis prophylaxis, *Nov.*, 742; *Jan.*, 1290  
 Kramm's approach to parapharyngeal abscess, *Jan.*, 1159  
 Krueger's pertussis vaccine, *Nov.*, 738, 739
- LACERATIONS of cervix, *Sept.*, 348  
*Lamblia intestinalis* in bile, *Nov.*, 680  
 Laryngeal neuralgia, superior, relief of, *Jan.*, 1029  
 Laryngitis, earache in, *Jan.*, 1055  
 Lavage, gastric, for diagnosis of tuberculosis, *Nov.*, 721  
 Lead neuritis, *Nov.*, 953  
 poisoning in children, convulsions from, *July*, 257  
 Leprous polyneuritis, *Nov.*, 958  
 Leukemia, chronic myelogenous, *Sept.*, 546, 549  
 Leukopenia, pernicious, *July*, 103-122  
 Leukorrhea, *Sept.*, 349  
 Lipemia, retinal, *Jan.*, 1233  
 Liver, active principle, *July*, 49, 75  
 storage of, *July*, 57, 58  
 extract, intra-osseous injection, in pernicious anemia, *July*, 50  
 extrinsic factor, *July*, 49, 51  
 functional tests, *Jan.*, 1165  
 therapy in secondary anemias, *July*, 96  
 Liver-stomach mixtures in pernicious anemia, *July*, 49
- Lobar pneumonia. See *Pneumonia*.  
 Lobectomy for bronchiectasis, *Jan.*, 1175  
 Löwenstein's culture medium in tuberculosis, *Nov.*, 722  
 Lumbago, relief of, *Jan.*, 1033-1038  
 Lumbar puncture in pseudo-uremic convulsions, *July*, 240  
 Lung, abscess of, bronchial obstruction in, *Sept.*, 456, 462  
 complicating pneumonia, *July*, 33, 34  
 carcinoma of, bronchial obstruction in, *Sept.*, 456  
 tuberculosis of. See *Tuberculosis, pulmonary*.  
 Lupus erythematosus, acute disseminated, visceral lesions of, *July*, 333-346  
 of scalp, *Jan.*, 1242  
 miliaris disseminatus faciei, *Sept.*, 617  
 Lyon's test in gallbladder disease, diagnostic value, *Nov.*, 679
- MACULA lutea, *Jan.*, 1200  
 Malignant hypertension, *July*, 134  
 tumors, roentgen treatment, *Sept.*, 598-603  
 Mantoux tuberculin test, *Nov.*, 703  
 March foot, *Jan.*, 1075  
 Marmite in pernicious anemia, *July*, 52, 54, 55, 56, 73  
 Marschik's approach to parapharyngeal abscess, *Jan.*, 1158  
 Massage, prostatic, *Jan.*, 1181, 1184  
 Mastoiditis, pain of, relief, *Jan.*, 1044-1047  
 Maxillary sinus infection, pain in, *Jan.*, 1062  
 McBurney's point symptoms in appendicitis, *July*, 190  
 Measles, immunization, *Nov.*, 734, 735; *Jan.*, 1287  
 Meckel's diverticulum, *Sept.*, 372, 373  
 Mediastinitis, pain in, simulating coronary disease, *Jan.*, 1079  
 Memory impairment, menopausal, *July*, 217  
 Meningitis, *Nov.*, 751-769  
 Menopause, symptoms and treatment, *July*, 205-226  
 Menorrhagia, menopausal, *July*, 214  
 Menstrual disturbance, functional, metrorrhagic type, in young women, *Sept.*, 359-364  
 Mental attitude in inoperable cancer, *July*, 196  
 disorders, puerperal, *Nov.*, 927-941  
 Mercury polyneuritis, *Nov.*, 955

- Metabolic disturbances in gallbladder disease, *Nov.*, 664  
 of pituitary gland, *Nov.*, 832  
 Middle ear disease, pain in, *Jan.*, 1041  
 Migraine, relief of, *Jan.*, 1015  
 Miliary tuberculosis, roentgen findings, *Nov.*, 712  
 Milk, evaporated, for infants, *Nov.*, 787  
 Moebius' sign, *Jan.*, 1208  
 Moro tuberculin test, *Nov.*, 703  
 Mosher's approach to parapharyngeal abscess, *Jan.*, 1158  
 Motor education, corrective, in birth injuries and allied problems, *Nov.*, 807-815  
 Mouth care in pneumonia, *July*, 16  
 Mucous colitis, *Jan.*, 1123, 1128  
 membrane of mouth, atrophy of, *July*, 59  
 Mumps, *Nov.*, 736  
 immunization, *Jan.*, 1290  
 Myoma of small intestine, *Sept.*, 371  
 Myringotomy, *Jan.*, 1042
- NABOTHIAN cysts, *Sept.*, 349  
 Nausea in acute appendicitis, *July*, 186, 193  
 in inoperable cancer, treatment, *July*, 200  
 Neosynthalin as insulin substitute, *Nov.*, 803  
 Nephritis, chronic glomerular, with mild nephrosis, hypertension, heart failure and pericarditis, *July*, 171-176  
 eye symptoms, *Jan.*, 1235  
 Nephrosis, amyloid, proteosuria in, *July*, 177-184  
 complicating chronic glomerular nephritis, *July*, 171  
 Nervous system, syphilis of, fever therapy, *Sept.*, 590  
 vegetative, rôle in climacteric, *July*, 210  
 Neufeld reaction for pneumococcus types, Sabin's technic, *July*, 3, 4  
 Neuralgia, dental causes, *Jan.*, 1063  
 glossopharyngeal, relief of, *Jan.*, 1028  
 laryngeal, superior, relief of, *Jan.*, 1029  
 occipital, relief of, *Jan.*, 1030  
 Sluder's, relief of, *Jan.*, 1031  
 trigeminal, relief of, *Jan.*, 1017-1028  
 Neurasthenia, traumatic, *Nov.*, 838, 839  
 Neurectomy, retrogasserian, for trigeminal neuralgia, *Jan.*, 1028
- Neuritis, multiple. See *Polyneuritis*.  
 optic, in brain abscess, *Jan.*, 1215  
 Neurological manifestations of pernicious anemia, with treatment, *July*, 79-89  
 Neuropsychoses, menopausal, *July*, 216  
 puerperal, *Nov.*, 927-941  
 Nevi, spider, *Sept.*, 536  
 Newborn, immunity in, *Nov.*, 733  
 Night blindness in gastro-intestinal disease or abnormality, *Sept.*, 468, 469  
 Nitroglycerin in angina pectoris, *Nov.*, 882, 883; *Jan.*, 1099  
 Nona, eye symptoms, *Jan.*, 1228  
 Nutritional anemia, *July*, 37-77
- OBESITY, pituitary, *Nov.*, 827, 832  
 Occipital neuralgia, relief, *Jan.*, 1030  
 Ophthalmoplegia in epidemic encephalitis, *Jan.*, 1228  
 Ophthalmoscopic test, *Jan.*, 1198  
 Optic disk, *Jan.*, 1200  
 neuritis in brain abscess, *Jan.*, 1215  
 Organotherapy in pituitary disorders, *Nov.*, 818  
 Osteo-arthritis of spine, pain of, simulating angina pectoris, *Jan.*, 1077  
 Otalgia, *Jan.*, 1039  
 Otitis media, pain in, relief, *Jan.*, 1041-1048  
 Otodynia, *Jan.*, 1039  
 Otomycosis, *Jan.*, 1050  
 Ovarian factor in menopause, *July*, 205  
 Ovarian-pituitary interrelationship, *July*, 206  
 Oxygen therapy in pneumonia, *July*, 9-12
- PAIN, abdominal, clinical significance and relief, *Jan.*, 1113-1129  
 severe, following emotional storm, *Sept.*, 399-402  
 in acute appendicitis, *July*, 186, 190  
 in dental field, *Jan.*, 1057-1066  
 in inoperable cancer, control of, *July*, 198  
 in pelvic lesions of female, relief, *Jan.*, 1122, 1131  
 in peptic ulcer, *Jan.*, 1120, 1126  
 in pneumonia, treatment, *July*, 13  
 relief of, symposium on, *Jan.*, 1013  
 shoulder, in gallbladder disease, *Nov.*, 651  
 simulating pain of coronary disease, *Jan.*, 1077-1083  
 Painful feet, relief of, *Jan.*, 1067-1075

- Palpitation, menopausal, *July*, 216  
 Pancreas, disease of, associated with gallbladder disease, *Nov.*, 664  
 Pancreatic ferments, *Nov.*, 683  
 Paracentesis of ear drum, *Jan.*, 1042  
 Paralysis from birth injuries and allied disorders, corrective motor education, *Nov.*, 807-815  
     infantile. See *Poliomyelitis*.  
     jake or ginger, *Nov.*, 953  
 Parapharyngeal space infections, *Jan.*, 1152  
 Parry's disease, eye symptoms, *Jan.*, 1204  
 Parasites in bile, *Nov.*, 680  
 Parental serum in measles, *Nov.*, 735  
 Paresthesia, menopausal, *July*, 217  
 Paroxysmal tachycardia, *Nov.*, 857-863  
 Patch test in contact eczema, *July*, 323  
 Pediculi, itching due to, *Nov.*, 976  
 Pellagra, *July*, 60-62  
     in gastro-intestinal disease or abnormality, *Sept.*, 468, 470  
     vitamin deficiency in, *Sept.*, 478  
 Pelvic abscess, gonorrheal, *Nov.*, 921  
     inflammatory disease, gonorrheal, *Nov.*, 920  
     lesions in female, pain of, relief, *Jan.*, 1122, 1131  
     sympathectomy, *Jan.*, 1136  
 Peptic ulcer, pain in, *Jan.*, 1120, 1126  
     perforation of, pain in, simulating coronary disease, *Jan.*, 1082  
     recurrent, reactivated and anastomotic, *Sept.*, 429-452  
 Periapical infection, pain in, *Jan.*, 1059  
 Pericarditis, acute fibrinous, simulating coronary disease, *Jan.*, 1078  
     complicating chronic glomerular nephritis, *July*, 171  
     uremic, *July*, 238  
 Perichondritis, auricular, *Jan.*, 1051  
 Peritoneal puncture in pneumococcus peritonitis, *Nov.*, 851, 852  
 Peritonitis, pneumococcus, *Nov.*, 847, 855  
     peritoneal puncture in, *Nov.*, 851, 852  
     postoperative, vaccination against, *Sept.*, 620  
 Pernicious anemia. See *Anemia, pernicious*.  
     leukopenia, *July*, 103-122  
 Peroneal sign in tetany, *July*, 255  
 Pertussis. See *Whooping cough*.  
 Petit mal, *July*, 260  
 Petroff's stool examination in tuberculosis, *Nov.*, 721  
 Pharyngomaxillary space infections, *Jan.*, 1152  
 Phenobarbital in angina pectoris, *Jan.*, 1104  
     in epilepsy, *July*, 262  
 Phrenicectomy for bronchiectasis, *Jan.*, 1175  
 Phytone, *Nov.*, 818  
 Picrotoxin poisoning, convulsions in, *July*, 245  
 Pigmentation in Addison's disease, *Sept.*, 387  
 Pink disease, *Nov.*, 957  
 Pitocin, *Nov.*, 819  
 Pitressin, *Nov.*, 819  
 Pituitary disorders, classification, *Nov.*, 821  
     eye symptoms, *Jan.*, 1239  
     treatment, *Nov.*, 817-835  
     extract, *Nov.*, 818  
     in Addison's disease, *Sept.*, 395  
     factor in menopause, *July*, 206  
     solution, *Nov.*, 819  
 Pituitary-ovarian interrelationship, *July*, 206  
 Pituitrin, *Nov.*, 819  
 Placental extracts in measles, *Nov.*, 734; *Jan.*, 1288  
 Pleural effusion in pulmonary tuberculosis, rapid development, *Nov.*, 907  
 Pleurisy, fibrinous, pain in, simulating coronary disease, *Jan.*, 1081  
     diaphragmatic, abdominal pain in, *Jan.*, 1115  
 Plummer-Vinson's syndrome, *July*, 71  
 Pneumococcus peritonitis, *Nov.*, 847-855  
     types, determining, *July*, 3, 4  
 Pneumolysis, perforation of lung following, *Nov.*, 909  
 Pneumonia, abdominal pain in, *Jan.*, 1115  
     artificial pneumothorax in, *July*, 19-27  
     digitalization in, *July*, 14  
     nursing care and diet in, *July*, 15-18  
     oxygen therapy, *July* 9-12  
     pain in, simulating coronary disease, *Jan.*, 1081  
     specific therapy, *July*, 3-9  
     surgical complications, *July*, 29-35  
     symptomatic treatment, *July*, 12-14  
 Pneumothorax, artificial, air embolism during, *Nov.*, 908  
     in hemoptysis of pulmonary tuberculosis, *Nov.*, 904  
     in lobar pneumonia, *July*, 19-27  
     spontaneous, in pulmonary tuberculosis, treatment, *Nov.*, 904-907  
     pain in, simulating coronary disease, *Jan.*, 1080

- Poliomyelitis, acute anterior, immunization, *Jan.*, 1290  
recent developments, *Nov.*, 740-744
- Politzer bag ear inflation, *Jan.*, 1042
- Polyneuritis, *July*, 68; *Nov.*, 943  
treatment, *Nov.*, 943-958  
vitamin deficiency in, *Sept.*, 478, 481
- Post cautery in gonorrhea of cervix, *Nov.*, 915
- Postoperative arthritis, acute, identification of, *Sept.*, 560-566  
prevention and treatment, *Sept.*, 566-573  
gas pains, *Jan.*, 1125
- Postural hypotension, *Nov.*, 868
- Postvaccinal encephalitis, *Jan.*, 1280
- Potassium iodide in angina pectoris, *Jan.*, 1104
- Pregnancy, anemia of, *July*, 38, 65  
heart disease in, management, *Nov.*, 893-899  
kidney disorders in, prevention, *July*, 295-299  
polyneuritis, *Nov.*, 953
- Preoperative vaccination against peritonitis, *Sept.*, 620, 626
- Prize fighter ear, *Jan.*, 1053
- Proctitis, gonorrheal, *Nov.*, 921
- Prolactin, *Nov.*, 819
- Prolan, *Nov.*, 818
- Proluton in functional metrorrhagia in young women, *Sept.*, 361
- Prostate gland, rectal palpation, *Jan.*, 1181
- Prostatic massage, *Jan.*, 1181, 1184
- Prostatitis, *Jan.*, 1181
- Proteosuria in amyloid nephrosis, *July*, 177-184
- Pruritus, *Nov.*, 971-980  
in Hodgkin's disease, *Sept.*, 426; *Nov.*, 967-970  
treatment, *Nov.*, 980-987
- Pseudonarcotism at menopause, *July*, 218
- Pseudo-uremia, *July*, 236, 238  
convulsions of, *July*, 238-241
- Psychic effect of abdominal trauma, *Nov.*, 837-845
- Psychoanalysis in puerperal psychoses, *Nov.*, 941
- Psychoses, menopausal, *July*, 216, 218  
puerperal, *Nov.*, 927-941
- Puerperal polynucleuritis, *Nov.*, 957
- Psychoses, *Nov.*, 927-941
- Pulmonary. See also *Lungs*.  
embolism simulating coronary disease, *Jan.*, 1079
- Pulpitis, pain in, *Jan.*, 1057
- Pupel tests, *Jan.*, 1196
- Purin derivatives in nephritis with vascular and cardiac complications, *July*, 175
- Pyemia following tonsillar infections, treatment, *Jan.*, 1151
- Pyloroplasty for peptic ulcer, recurrence after, *Sept.*, 440
- Pyrexia in children, convulsions due to, *July*, 252
- QUININE in paroxysmal tachycardia, *Nov.*, 861  
in pneumonia, *July*, 6
- RABIES, immunization, *Jan.*, 1290
- Radium treatment of functional metrorrhagia in young women, *Sept.*, 363
- Raynaud's disease, treatment, *July*, 148
- Rectum, gonorrhea of, *Nov.*, 921
- Renal colic, *Jan.*, 1119, 1124
- Resistance to infections, vitamins and, *Sept.*, 471
- Respirator in poliomyelitis, *Nov.*, 743
- Rest in angina pectoris, *Jan.*, 1097  
in hypertension, *July*, 143  
in pneumonia, *July*, 15  
in tuberculosis, *July*, 228, 230
- Reticulocyte count in pernicious anemia, *July*, 40
- Retinal hemorrhages in diabetes, *Jan.*, 1234  
lipemia, *Jan.*, 1233  
vessels, examination, *Jan.*, 1201
- Retinitis, albuminuric, *Jan.*, 1236  
arteriosclerotic, *Jan.*, 1210  
diabetic, *Jan.*, 1232
- Rheumatism, gonorrheal, *Sept.*, 551
- Rhizotomy for essential hypertension, *Sept.*, 523
- Ribs, fracture of, pain in, simulating coronary disease, *Jan.*, 1081
- Rickets, dietetic factor, *Jan.*, 1291-1304  
tetany due to, *July*, 255  
vitamin deficiency in, *Sept.*, 478, 483
- Ringworm of scalp, *Jan.*, 1241-1250
- Roentgen diagnosis of tuberculosis in children, *Nov.*, 706-721
- epilation of scalp, *Jan.*, 1246
- treatment of inflammatory and malignant conditions, *Sept.*, 597-603  
of pruritus, *Nov.*, 983
- Rupture of ear drum, traumatic, *Jan.*, 1054

- SABIN's technic for Neufeld reaction for pneumococcus types, *July*, 3, 4
- Salpingitis, gonorrheal, *Nov.*, 919, 920
- fever therapy, *Sept.*, 588, 590
- Salt therapy in Addison's disease, *Sept.*, 391; *Nov.*, 959-965
- Sarcoma of small intestine, *Sept.*, 370
- Sauer's pertussis vaccine, *Nov.*, 738; *Jan.*, 1288
- Scalp, ringworm and related lesions of, *Jan.*, 1241-1250
- x-ray epilation, *Jan.*, 1246
- Scarlet fever, *Nov.*, 739
- Dick test, *Jan.*, 1285
- immunization, *Jan.*, 1285
- Schick test, *Jan.*, 1282
- School problems in diabetes, *July*, 282
- Sciatica, relief of, *Jan.*, 1033-1038
- Scurvy, vitamins and, *Sept.*, 478
- Sedimentation test in tuberculosis in children, *Nov.*, 724
- Sepsis following tonsillar infections, treatment, *Jan.*, 1151
- Septic sore throat, clinical and bacteriological considerations, *Jan.*, 1143
- Serum prophylaxis of poliomyelitis, *Nov.*, 742; *Jan.*, 1290
- reaction in meningitis, *Nov.*, 766
- treatment of meningitis, *Nov.*, 760
- of pneumonia, *July*, 3-6
- Sexual desire and hypertension, *July*, 146
- Shoulder pain in gallbladder disease, *Nov.*, 651
- Simmond's disease, *Nov.*, 825
- Sinus, maxillary, disease of, pain in, *Jan.*, 1062
- Sistomensin in functional metrorrhagia in young women, *Sept.*, 361
- Skene's glands, gonorrheal inflammation, *Nov.*, 922
- Skin, tuberculosis of, *Sept.*, 611-618
- tumors of, roentgen therapy, *Sept.*, 599
- Skull fractures, eye symptoms, *Jan.*, 1238
- Sleeping sickness, eye symptoms, *Jan.*, 1228
- Sluder's neuralgia, relief of, *Jan.*, 1031
- Smallpox, vaccination, *Jan.*, 1277
- Snellen test types, *Jan.*, 1190
- Sore throat, septic, clinical and bacteriological considerations, *Jan.*, 1143
- Spasmophilia, *July*, 254
- Speech disturbances in birth injuries, *Nov.*, 810, 812
- Spider nevi, *Sept.*, 536
- Spinal fluid examinations in meningitis, *Nov.*, 758
- Spine, osteo-arthritis of, pain in, simulating angina pectoris, *Jan.*, 1077
- Splenectomy for pernicious anemia, *July*, 44
- value of, in jaundice from atypical blood dyscrasias, *Sept.*, 550
- Sprue, *July*, 62-64
- Stasis-edema in thrombophlebitis, *Sept.*, 542
- in varicose veins, *Sept.*, 538
- Status epilepticus, *July*, 261
- Steatorrhea, idiopathic, *July*, 66
- Stellwag's sign, *Jan.*, 1208
- Stokes-Adams attacks, *July*, 243
- Stomach, carcinoma of, inoperable, *July*, 195
- in development of pernicious anemia, *July*, 40
- secretory, motor and sensory disturbances in gallbladder disease, *Nov.*, 660-662
- Stools, Petroff's examination in tuberculosis, *Nov.*, 721
- Streptococcic sore throat, *Jan.*, 1143
- Stridor, significance in tracheal and bronchial obstruction, *Sept.*, 454
- Strychnine poisoning, convulsions in, *July*, 244, 256
- Subperichondrial abscess, *Jan.*, 1051
- Suburethral abscess, gonorrheal, *Nov.*, 922
- Suprarenal glands in Addison's disease, *Sept.*, 384, 386, 390
- Sympathectomy, pelvic, *Jan.*, 1136
- Synthalin as insulin substitute, *Nov.*, 803
- Syphilis, eye symptoms, *Jan.*, 1239
- of nervous system, fever therapy, *Sept.*, 590
- TABES, eye symptoms, *Jan.*, 1238
- Tachycardia, paroxysmal, *Nov.*, 857-863
- Teeth, unerupted and impacted, pain due to, *Jan.*, 1062
- Telangiectases, *Sept.*, 536
- Temporomandibular joint diseases, pain in, *Jan.*, 1065
- Tension of eye, testing, *Jan.*, 1194
- Test types, visual, *Jan.*, 1190
- Testis, tumors of, roentgen treatment, *Sept.*, 599
- Tetanus, immunization, *Jan.*, 1284
- neonatorum, *July*, 251
- Tetany, *July*, 241-243
- infantile, *July*, 254
- Thallium acetate neuritis, *Nov.*, 955
- Theobromine in angina pectoris, *Jan.*, 1101

- Theophylline in angina pectoris, *Jan.*, 1101
- Throat, sore, septic, *Jan.*, 1143
- Thrombophlebitis, *Sept.*, 539-543
- Thrombosis, coronary, angina pectoris and, differentiation, *Jan.*, 1085  
treatment, *Nov.*, 873-880, 887  
of aorta and its larger branches, *July*, 159-170
- Thyroid gland, carcinoma of, roentgen therapy, *Sept.*, 600  
diseases, gastro-intestinal manifestations, *Jan.*, 1258
- Thyroidectomy for angina pectoris, *Jan.*, 1105
- Tic douloureux, relief of, *Jan.*, 1017
- Tinnitus, menopausal, *July*, 218
- Tissue extracts in angina pectoris, *Jan.*, 1103
- Tobacco, use of, in angina pectoris, *Nov.*, 883; *Jan.*, 1099
- Tongue, black, *July*, 59  
burning, *Jan.*, 1065
- Tonsillar infections, sepsis and pyemia following, treatment, *Jan.*, 1151
- Toothache, *Jan.*, 1057  
ear pain in, *Jan.*, 1055
- Toxoid, diphtheria, *Nov.*, 736; *Jan.*, 1281
- Trachea, obstruction of, clinical manifestations, with bronchoscopic observations, *Sept.*, 453-462
- Transfusions, blood, in functional metrorrhagia in young women, *Sept.*, 362  
in inoperable cancer, *July*, 202  
in secondary anemias, *July*, 99
- Trauma, abdominal, psychic effect, *Nov.*, 837-845
- Trendelenburg's test in varicose veins, *Sept.*, 536
- Trigeminal neuralgia, relief of, *Jan.*, 1017-1028
- Tropical macrocytic anemia, *July*, 66
- Trousseau's sign in tetany, *July*, 242
- Tuberculin reaction, *Nov.*, 702-706
- Tuberculosis, cutaneous, hematogenous type, *Sept.*, 611-618  
miliary, roentgen findings, *Nov.*, 712  
of small intestine, *Sept.*, 379  
of suprarenal glands in Addison's disease, *Sept.*, 384  
pulmonary, abdominal pain in, *Jan.*, 1116  
bronchial obstruction in, *Sept.*, 456  
crises in, management, *Nov.*, 901-909  
gastro-intestinal manifestations, *Jan.*, 1258
- Tuberculosis, pulmonary, home treatment, *July*, 227-231  
in children, diagnosis, *Nov.*, 701-729
- Tuberculous bronchopneumonia in children, *Nov.*, 717  
hilar nodes, *Nov.*, 711  
meningitis, *Nov.*, 758, 759
- Tumors, malignant, roentgen treatment, *Sept.*, 598-603  
of brain. See *Brain, tumors of.*  
of small intestine, *Sept.*, 366, 370  
of trachea causing obstruction, *Sept.*, 454  
pituitary, *Nov.*, 832
- Typhoid fever, immunization. *Jan.*, 1284
- ULCER, gastrojejunal, following gastroenterostomy, *Sept.*, 442  
of ileum, *Sept.*, 380  
peptic. See *Peptic ulcer.*  
varicose, *Sept.*, 539
- Ulceration, uremic, *July*, 238
- Ulcerative colitis, chronic, management, *Sept.*, 403-407  
two carcinomas complicating, *Sept.*, 408-410  
enterocolitis, regional, *Sept.*, 411-422
- Ultraviolet treatment of pruritus, *Nov.*, 983  
of secondary anemias, *July*, 98
- Unconsciousness in heart block, *July*, 243
- Urea frost, *July*, 237
- Uremia, *July*, 236-241  
convulsions in, *July*, 236  
in children, *July*, 258
- Uremic poisoning, treatment, *Jan.*, 1270
- Urethra, female, gonorrheal infection, *Nov.*, 912, 922  
stricture, *Nov.*, 925  
milking of, *Nov.*, 913
- Urethral caruncle, *Nov.*, 923
- Urethritis, gonococcal, fever therapy, *Sept.*, 588
- Urinary incontinence in children, *July*, 287-294  
tract diseases, gastro-intestinal manifestations, *Jan.*, 1253, 1255
- Uterine bleeding, menopausal, *July*, 214  
cervix, lesions of, *Sept.*, 347-357
- VACCINA, generalized, *Jan.*, 1279
- Vaccine, Krueger's pertussis, *Nov.*, 738, 739

- Vaccine prophylaxis of colds, *Nov.*, 749  
 Sauer's pertussis, *Nov.*, 738; *Jan.*, 1288  
 treatment of pneumonia, *July*, 6  
 Vaginal complications in gonorrhea, *Nov.*, 919  
 Valsalva ear inflation, *Jan.*, 1042  
 Van den Bergh reaction, *Jan.*, 1166  
 Varicose ulcers, *Sept.*, 539  
 veins, *Sept.*, 535-538  
 Vascular crises in hypertension, management, *July*, 133, 143  
 Vegex in pernicious anemia, *July*, 56, 73, 74  
 Veins, diseases of, *Sept.*, 535-543  
 Venesection in pseudo-uremic convulsions, *July*, 240  
 Venous pressure, *Jan.*, 1273-1276  
 Vertigo e vesica fellea laesa, *Nov.*, 653  
 in gallbladder disease, *Nov.*, 652  
 menopausal, *July*, 218  
 Virus diseases, *Nov.*, 732  
 Visceral lesions of acute disseminated lupus erythematosus, *July*, 333-346  
 Visual tests, *Jan.*, 1190, 1193  
 Vitamin B and pernicious anemia, *July*, 51, 74  
 factor in colds, *Nov.*, 748  
 therapy in secondary anemias, *July*, 97  
 Vitamins, chemical nature, *Sept.*, 477-485  
 practical considerations, *Sept.*, 463-476  
 Volvulus, *Sept.*, 378  
 Vomiting in acute appendicitis, *July*, 186, 193  
 in inoperable cancer, treatment, *July*, 200  
 Von Graefe's sign, *Jan.*, 1207  
 Vulvovaginal gland, gonorrhea of, *Nov.*, 919  
 WEAKNESS in inoperable cancer, treatment, *July*, 201  
 Westphal's sign, *Nov.*, 652  
 Whooping cough, *Nov.*, 732  
 vaccine prophylaxis and treatment, *Nov.*, 738, 739; *Jan.*, 1288  
 XEROPHTHALMIA and vitamin deficiency, *Sept.*, 478  
 YEASTS, autolyzed, in pernicious anemia, effects, *July*, 51-57  
 ZOSTER auriculæ, Hunt's, *Jan.*, 1052







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# CONTENTS

	PAGE
SYMPOSIUM ON RECENT ADVANCES IN TREATMENT.....	1319
Recent Advances in the Treatment of Heart Disease ..	1321
By Drs. PAUL D. WHITE and R. EARLE GLENDY	
Recent Advances in the Treatment of Arterial Hypertension..	1343
By DR. SOMA WEISS	
The Treatment of Gonococcal Arthritis, Rheumatoid Arthritis, and Gout	1367
By DR. CHESTER S. KEEFER	
Treatment of Diseases of the Thyroid... ..	1377
By DR. J. H. MEANS	
Treatment of Scarlet Fever and Diphtheria.... .	1389
By DR. CONRAD WESSELHOEFT	
Some Recent Advances in Vaccines and Serums: A Review....	1409
By DR. LEROY D. FOTHERGILL	
Recent Advances in Medical Gynecology .. . . .	1439
By DR. JOE VINCENT MEIGS	
Recent Advances in the Treatment of Hay Fever and Asthma ..	1467
By DR. ABRAHAM COLMES	
Recent Advances in Dietotherapy... ..	1493
By DR. EDWARD S. EMERY, JR.	
Certain Aspects of the Common Cold... ..	1499
By DR. FREDERICK T. LORD	
The Significance and Interpretation of Heart Murmurs in General Practice ..	1505
By DR. WILLIAM H. ROBEY	
The Diagnosis and Management of the Chronic Obstructive Type of Peptic Ulcer.....	1519
By DR. EDWARD S. EMERY, JR.	
The Clinical Importance of the Sequence of Events in Bone Marrow Failure ...	1525
By DR. HENRY JACKSON, JR.	
Pain in the Region of the Heart.....	1533
By Drs. LAURENCE B. ELLIS and BURTON E. HAMILTON	
The Curability of Pollen Hay Fever ...	1547
By DR. I. CHANDLER WALKER	
The Practical Management of Congestive Failure ..	1563
By DR. JAMES M. FAULKNER	
Syringomyelia—Diagnosis and Treatment ..	1571
By DR. TRACY J. PUTNAM	
Concerning Fits.....	1583
By DR. STANLEY COBB	
The Treatment of Insomnia ..	1597
By DR. G. P. GRABFIELD	
Abdominal Pain in Children. ....	1603
By DR. RICHARD M. SMITH	
The Clinical Significance and Treatment of Vertigo, Dizziness, and Related Symptoms.....	1617
By DR. EUGENE B. FERRIS, JR.	
Diseases of the Skin. ....	1627
By DR. JACOB H. SWARTZ	
The Treatment of Jaundice and Hepatic Insufficiency ..	1651
By DR. CHESTER M. JONES	
Prenatal Care in Private Practice ..	1659
By DR. FREDERICK C. IRVING	
Idiopathic Ulcerative Colitis in Children ..	1673
By Drs. WILLIAM E. LADD and LEROY D. FOTHERGILL	
The Clinical Significance of Problems of Absorption in the Human Gastro-Intestinal Tract. ....	1685
By DR. CLARK W. HEATH	
Cumulative Index ..	1695

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## SYMPOSIUM ON RECENT ADVANCES IN TREATMENT

The following clinics are included in this Symposium:

Paul D. White and R. Earle Glendy: RECENT ADVANCES IN THE TREATMENT OF HEART DISEASE.

Soma Weiss: RECENT ADVANCES IN THE TREATMENT OF ARTERIAL HYPERTENSION.

Chester S. Keefer: THE TREATMENT OF GONOCOCCAL ARTHRITIS, RHEUMATOID ARTHRITIS AND GOUT.

J. H. Means: TREATMENT OF DISEASES OF THE THYROID.

Conrad Wesselhoeft: TREATMENT OF SCARLET FEVER AND DIPHThERIA.

LeRoy D. Fothergill: SOME RECENT ADVANCES IN VACCINES AND SERUMS: A REVIEW.

Joe Vincent Meigs: RECENT ADVANCES IN MEDICAL GYNECOLOGY.

Abraham Colmes: RECENT ADVANCES IN THE TREATMENT OF HAY FEVER AND ASTHMA.

Edward S. Emery, Jr.: RECENT ADVANCES IN DIETOTHERAPY.



CLINIC OF DRS. PAUL D. WHITE  
AND R. EARLE GLENDY

FROM THE CARDIAC CLINICS AND LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL

---

RECENT ADVANCES IN THE TREATMENT OF HEART  
DISEASE

INTRODUCTION

DURING the past decade several significant advances have been made in the treatment of heart disease, probably more than in any previous decade. We have selected for presentation herewith, 5 cases, each illustrating one of the more important new therapeutic measures. In the order of discussion these five measures are quinidine therapy, the use of salyrgan or mercupurin, paravertebral alcohol injection, total thyroidectomy and pericardial resection. They are important adjuncts in treatment but by no means replace any of the reliable older methods of cardiac therapy which include rest, restriction of fluids and diet, the proper use of digitalis, of vasodilator drugs, and of diuretics by mouth, and the cardiac bed and Southey tubes, merely to mention the more important time-honored methods.

One other new therapeutic measure which deserves honorable mention at least, even if not so important as those that are presented in detail in this report, is the administration of theophyllin-ethylene-diamine (ordinarily called aminophyllin, euphyllin, or metaphyllin) in the relief of Cheyne-Stokes respiration and obstinate recurrent angina pectoris (especially at rest). In such cases rapid and striking relief may sometimes follow the administration of  $7\frac{1}{2}$  grains (2 cc. ampule) of aminophyllin intramuscularly, or 4 grains (10 cc. ampule) intravenously, or less satisfactorily  $1\frac{1}{2}$  to 3 grains by mouth, two to five times daily.



## QUINIDINE THERAPY

**Case I.**—J. L., a Jewish boy aged nineteen years, was admitted to the Massachusetts General Hospital on February 28, 1935, complaining of rapid irregular palpitation and some vomiting of four months' duration. He had had whooping cough and measles in childhood. In May, 1925, several months after an infection with fever and vomiting, he was seen by us and found to have rheumatic heart disease, with well-marked cardiac enlargement, mitral stenosis, aortic regurgitation, and a normal rhythm with a rate of 96 beats per minute. In June, 1925, a tonsillectomy was done. In the fall of 1925, on account of persistent signs of rheumatic activity (increased temperature, pulse, and white blood cell count), he was put to bed and kept there for about six months, during which time he continued to have a rapid pulse rate, at times as high as 140. From June, 1926 to November, 1934 he felt fairly well, except for an occasional respiratory infection, and with restricted activity was able to attend school and lead a fairly normal life. His heart gradually increased in size, but the rhythm remained normal. During November, 1934, following a cold, he noticed, for the first time, rapid irregular palpitation. He was digitalized at this time and given a maintenance dose of digitalis. For the next three months he did not feel well. On the days when the palpitation was most noticeable he felt weak and often vomited almost everything eaten. Early in December, 1934 he spat  $\frac{1}{2}$  ounce of bright red blood, and two weeks later again raised the same amount of blood. From that time until his admission to the hospital, he was confined to bed and chair except for an occasional short walk. The distressing palpitation continued. There was no dyspnea, orthopnea, or edema. His physician referred him to the hospital because of a persistently rapid pulse rate, which did not respond even to large doses of digitalis and small doses of quinidine at home.

Physical examination showed a fairly well nourished, somewhat pale young man with anxious facies sitting propped up in bed. Breathing was slightly rapid. There were rapid irregular arterial pulsations in the neck. The pupils were somewhat dilated but reacted normally. There were a few slightly enlarged nontender axillary lymph glands. The precordium bulged slightly. The heart was greatly enlarged downward and to the left, the left border of dullness lying in the midaxillary line. The apex impulse was forceful and easily visible in the seventh interspace. The first sound at the apex was slapping in quality and preceded by a mid- and late-diastolic rumble. There was also a short systolic murmur at the apex. Along the left sternal border a faint early blowing diastolic murmur was audible. The rhythm was totally irregular at a rate of 160 beats per minute. The blood pressure was 154 mm. mercury systolic and 20 diastolic. The liver was palpable 4 cm. below the costal margin in the nipple line. There were no rheumatic nodules and no cyanosis or edema.

The urine was normal on two occasions. The hemoglobin was 80 per cent (T), the red blood cell count was 5,220,000 and the white count was 21,430. The corrected sedimentation rate was 0.57 mm. per minute. The Hinton reaction was negative. The electrocardiogram showed auricular fibrillation with a ventricular rate varying from 120 to 180. The basal metabolic rate on six occasions, after his rapid pulse rate was controlled, ranged from -1 per cent to -19 per cent, three times less than -10 and three times greater than -10.

The accompanying chart (Fig. 164) shows his course while in the hospital, including temperature, apex and radial pulse rates, respirations, medications, sedimentation rate, and white blood cell counts. Digitalis was discontinued

on the second day because of nausea. It was not certain whether he had had too much digitalis or was simply nauseated from congestion in the gastrointestinal tract. On the morning of the third day after admission following the administration of 30 grains of quinidine sulphate in divided doses of 6 grains each in twenty-four hours for two days, the pulse rate dropped from 130 to 80 beats per minutes and the rhythm became fundamentally regular, with much subjective relief of symptoms. Thereafter, while in the hospital, the pulse rate ranged from 80 to 90, occasionally rising to 100 or slightly above. The slight discrepancy in apex and radial rates after the auricular fibrillation ceased was due to premature beats. On account of evidence of ac-

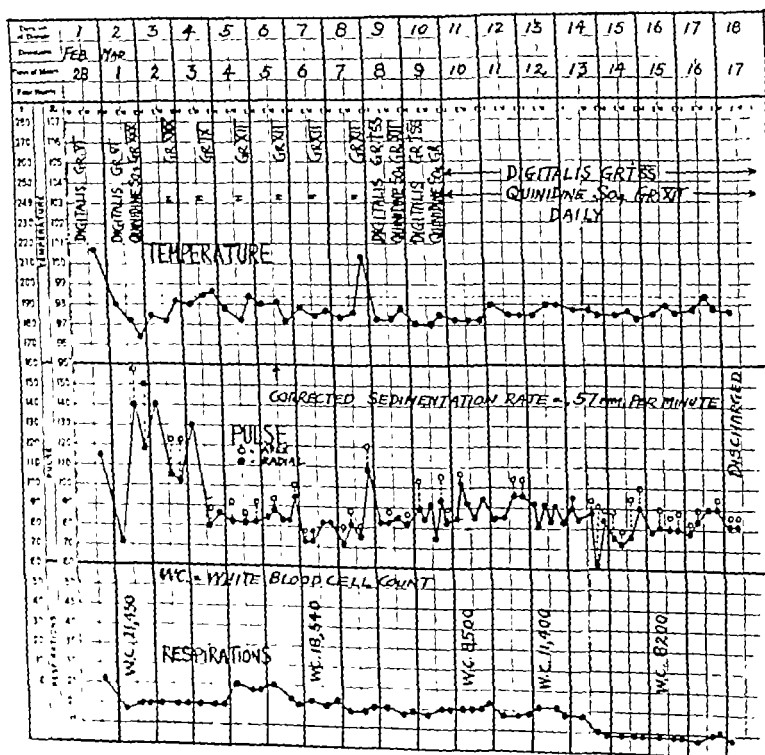


Fig. 164.—Case I.

tive rheumatic infection, which, no doubt, made the auricular fibrillation so refractory to treatment, he was kept quietly in bed and advised to remain in bed for several weeks on his return home. He was discharged, much improved, on a ration of 12 grains of digitalis and 12 grains of quinidine sulphate daily in divided doses of 6 grains each. His basal metabolic rate on one occasion after leaving the hospital was plus 30 per cent. This was checked with total thyroidectomy in mind as a possible therapeutic procedure.

He was last seen on September 6, 1935, five months after his discharge from the hospital. Following his discharge he remained quiet for several weeks and continued on a daily ration of digitalis, 12 grains, and quinidine sulphate

3 grains, four times a day, for nearly three months. He improved remarkably and was able to work almost every day through the summer as an announcer at an amusement park. The digitalis was omitted and the dosage of quinidine sulphate reduced to 6 grains daily, 3 grains in the morning and 3 grains at night.

Physical examination on September 6, 1935, showed his skin well tanned and his general condition good. The apex impulse of the heart was visible and palpable in the seventh intercostal space 12.5 cm. to the left of the mid-

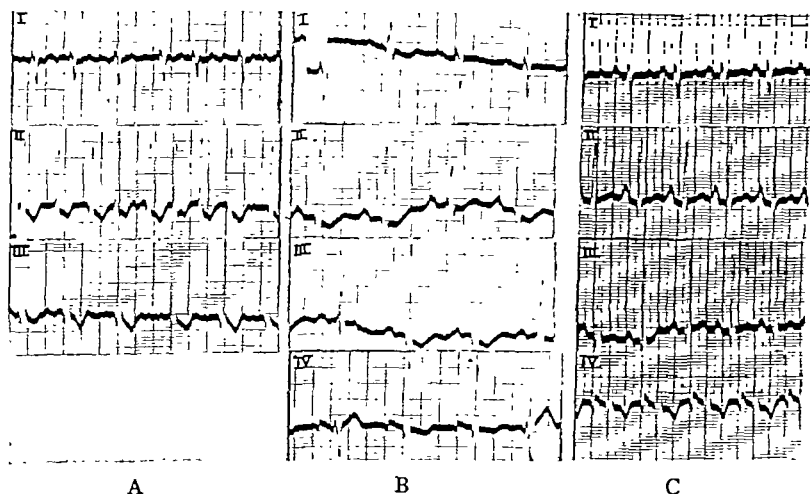


Fig. 165.—Case I. *A*, February 28, 1935. Fully digitalized but before intensive quinidine therapy. Auricular fibrillation, ventricular rate 120–180, well-marked right axis deviation, and deeply inverted S-T segments in Leads II and III. *B*, March 3, 1935. After quinidine sulphate in divided doses of 6 grains each five times a day for two days (60 grains in all). Normal rhythm, rate 80, interrupted every third beat by an abnormal QRS complex, probably a late premature beat. Prolonged P-R interval (0.23 seconds), right axis deviation, and persistent digitalis effect upon the S-T segments. *C*, September 6, 1935. After a fairly active summer. No digitalis for several months. Quinidine sulphate, 3 grains, twice daily, morning and night. Normal rhythm, rate 100, slightly prolonged P-R interval (0.21 seconds), prominent P2, low but upright T waves in the conventional leads (disappearance of digitalis effect), and right axis deviation.

sternal line. There were moderate aortic systolic and diastolic murmurs, a slight to moderate apical middiastolic murmur, and a loud apical systolic murmur. The blood pressure was 140 systolic and 60 diastolic. The lungs were clear, the liver was not enlarged, and there was no edema over the shins or ankles. He was advised to carry on quietly, using 3 grains quinidine, twice daily, or more often if necessary, and, if possible, to spend the winter in a milder climate.

Figure 165 shows serial electrocardiograms during and following the auricular fibrillation.

**Discussion.**—So long ago as 1749 quinine was reported by Senac to be helpful in the control of rebellious palpitation, but it was used very irregularly and by most internists not at all, until about fifteen years ago, when its isomer quinidine was introduced by Frey,<sup>1</sup> after he had learned of the accidental discovery (by a patient of Professor Wenckebach's) of the beneficial effect of quinine in controlling paroxysmal auricular fibrillation.

Fifteen years ago quinidine was tried out in a large number of unselected cases of auricular fibrillation. Frequently it restored normal rhythm, but there were many failures and a few disasters which resulted in considerable dissatisfaction or actual fear in the use of the drug.

During the past ten years, however, in carefully selected cases, quinidine sulphate has been found useful and, at times, even life saving, as in our Case I, recounted above, who undoubtedly would have gone on to extensive congestive failure and death had there been a persistence of the uncontrolled ventricular rate in his obstinate auricular fibrillation.

There are three indications for quinidine therapy. In the first place it may save lives by the restoration of normal rhythm in cases of auricular fibrillation or paroxysmal ventricular tachycardia in the presence of serious heart disease (including coronary thrombosis) when other measures have failed. Secondly, it may restore normal rhythm in cases of persistent auricular fibrillation who show little or no heart disease, especially when they are uncomfortable as a result of the palpitation caused by the arrhythmia. And thirdly, in rations it may prevent disturbances of rhythm, particularly paroxysms of auricular fibrillation and also sometimes paroxysmal tachycardia and premature beats.

For the control of auricular fibrillation or paroxysmal ventricular tachycardia a good method of quinidine treatment has, in our hands, been to administer 6 grains of quinidine sulphate every two hours for five doses on a given day following a test dose of 3 grains (to detect any unusual sensitivity to the drug). This program of 30 grains of quinidine sulphate divided into five doses over a period of eight hours usually suffices to restore normal rhythm, but if the abnormal rhythm persists the program can be extended cautiously to include

one to two more doses in two to four hours, or it may be repeated the next day. Patients receiving these large doses of quinidine sulphate should be in bed under close observation and preferably with electrocardiographic control (for example, an electrocardiogram should be taken before starting quinidine, before the third dose, and before the fifth dose). Mild toxic symptoms such as slight tinnitus are not important, but severe symptoms of cinchonism, excessive tachycardia (over 150 per minute), or intraventricular block by electrocardiogram demand the omission of the drug.

Finally in the prevention of arrhythmias, rations of 3 or rarely 6 grains of quinidine may be taken one to four times a day (even at three hour intervals) for periods of days or weeks. The effect of a single dose lasts about four hours. Therefore, it is important to prescribe quinidine an hour or so before some particular effort or episode which might excite an attack of tachycardia or fibrillation. Looseness of the bowels (sometimes a favorable laxative effect) or a little deafness occasionally results from the long continued use of quinidine sulphate and may require omission of the drug or reduction in the dosage.

#### SALYRGAN

**Case II.**—A. E. B., a seventy-one-year-old merchant, till June in good health, was admitted to the Baker Memorial Hospital in September, 1932. His first serious symptoms had appeared three months previously while driving his car home from a family dinner. At the onset he complained of indigestion. After several hours he vomited and later developed a feeling of pressure in his chest and difficulty in breathing. He preferred to sit upright by the open window. He coughed and raised blood-tinged sputum. Respiration was wheezing in character. He remained strictly in bed for several days following this episode and had spent the greater part of his time in bed thereafter, though he drove his car on two occasions. Approximately nine weeks after the onset of symptoms he was found in a stuporous condition, thought to be uremic coma, from which he recovered in a few days. Coincidentally edema of the legs appeared and breathing became increasingly more difficult up to the time he was seen by us, in spite of a fair amount of digitalis and diuretics by mouth.

Physical examination revealed an elderly man who apparently had lost weight but who showed extensive edema of the legs, genitalia, and trunk. Breathing was somewhat rapid and labored. The pupils reacted normally. The upper teeth were replaced by a denture. Many lower teeth were missing. The tongue and buccal mucous membrane were bright red and moist; the tongue was sore. The heart apex and left border of dullness were in the sixth intercostal space, 13 cm from the midsternal line and well outside the mid-clavicular line. The heart sounds were of poor quality, the rhythm was regular except for an occasional premature beat, the rate was 86 beats per minute,

and there were no murmurs. The blood pressure was 128 mm. mercury systolic and 98 diastolic. There was evidence of a considerable quantity of fluid in the right chest, and many moist râles were found in the left lower lung. The liver was enlarged, extending 6 cm. below the costal margin, and there was moderate ascites.

The urine on several occasions showed the slightest possible trace of albumin and several white and red blood cells; the specific gravity varied from 1.014 to 1.018. The nonprotein nitrogen of the blood was 34 mg. per cent. The hemoglobin was 75 per cent (T), the red blood count was 5,050,000, and the white count was 12,700. The differential count and smear were normal.

The electrocardiogram showed ventricular premature beats interrupting an otherwise normal rhythm, rate of 90, P-R interval prolonged, 0.22 second, slightly slurred Q-R-S waves, and low T waves.

The severe congestive failure was thought to be the result of long-standing hypertension and attendant coronary disease. The prognosis was considered quite grave and it seemed that even with the best treatment his anasarca could be but temporarily controlled.

The accompanying chart (Fig. 166) shows at a glance the extensive therapy he received while in the hospital, including venesection, thoracentesis, digitalis, the xanthine diuretic theocalcin, and the mercurial diuretic salyrgan. His response to treatment was far beyond expectations and as the hydrothorax and edema cleared he improved gradually. Near the end of his hospital stay he was able to be fairly active, walking about, without dyspnea and free of edema except for very slight pitting of both feet posteriorly.

Following his discharge from the hospital on December 14, 1932, after an eleven weeks' stay, he did fairly well at home under a quiet régime, a maintenance dose of digitalis, and salyrgan two or three times a month. A constant low grade of congestive failure persisted, however, and varied with the response to diuretics.

One year following the onset of his original symptoms he was admitted to the hospital again on account of increasing congestive failure, weakness, and mental confusion. At this time he was quite dyspneic, and the respirations were of the Cheyne-Stokes variety. The lips and tongue were cyanotic. The cervical and arm veins were engorged. The heart apex impulse and left border of dulness were 12 cm. to the left of the midsternal line in the sixth intercostal space. There was a slight gallop rhythm at the apex and marked slowing of the heart rate with audible auricular sounds during the periods of hyperpnea, probably the result of an increase in A-V block (shown to be present by electrocardiogram). The pulmonic second sound was slightly accentuated. There were no murmurs. The blood pressure was 130 systolic and 80 diastolic. There was a moderate amount of fluid in the right chest and in the abdomen. The liver was engorged and palpable, 6 cm. below the costal margin. There was edema over the flanks and of the ankles. The electrocardiogram showed an unusual ectopic auricular tachycardia at a rate of 170 with varying degrees of A-V block (2:1 and 4:1) and a ventricular rate ranging from 42 to 84, also low voltage and a rare ectopic ventricular beat. The urine on two occasions showed a very slight trace of albumin and a low specific gravity (1.002 to 1.010). The blood counts and hemoglobin were normal. The nonprotein nitrogen of the blood was 44 mg. per cent on admission and 32 mg. per cent one week after admission.

His treatment on this occasion, was, for the most part, as it had been previously (rest, digitalis, theocalcin, and salyrgan). His response was good to the extent that his edema cleared but he remained quite weak and mentally

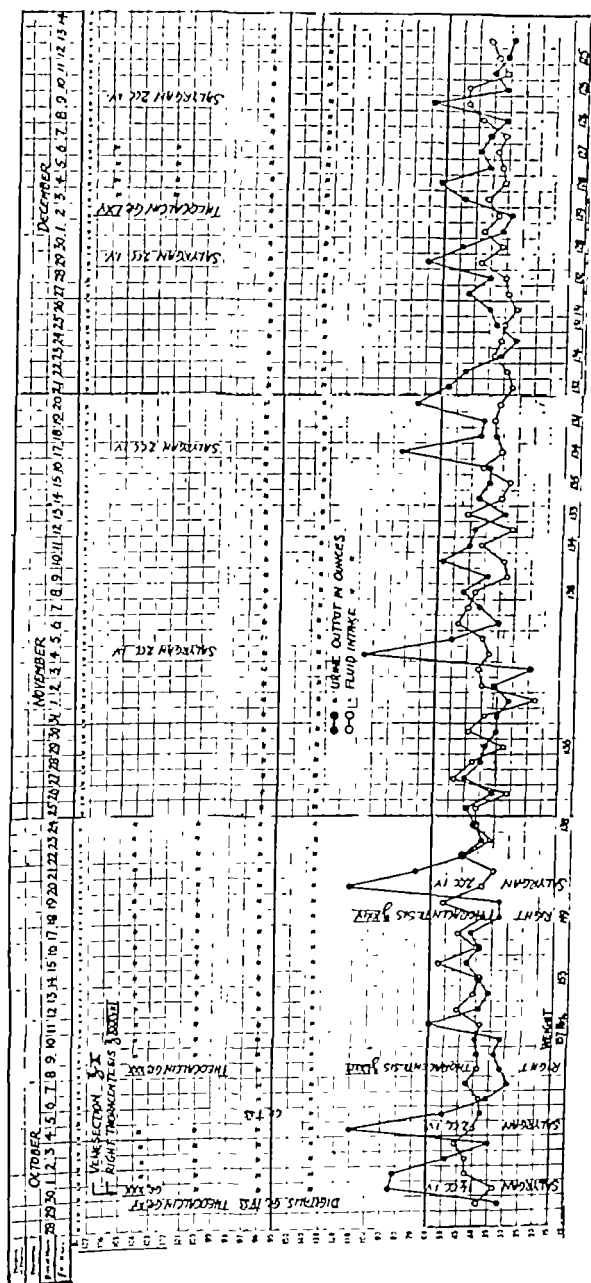


Fig. 166.—Case II.

confused. He was discharged at the end of five weeks somewhat improved but his condition thereafter grew steadily worse and two weeks later he died of

progressive congestive failure and general debility after remaining in coma for two days. He survived longer than we had expected him to do when we first saw him.

**Discussion.**—Salyrgan or mersalyl, a preparation of mercury in solution for intravenous or intramuscular injection has proved a great boon in the last decade as a vigorous safe diuretic in the control of the intractable congestion due to heart failure or even other cause (such as chronic constrictive pericarditis, in preparation for operation). Its use is a refinement developed from the giving of mercury by mouth introduced many years ago for diuretic purposes and the accidental discovery by Saxl<sup>2</sup> in 1920 of the diuretic properties of mercury given intravenously to a syphilitic patient with edema. One of the original preparations novasural (merbaphen) was much less effective and more toxic. A newer preparation, mercupurin (novurit), has been introduced, which in a few patients is more effective than salyrgan and may be substituted for it in the same dosage. Mercupurin contains mercury and theophyllin which also acts as a diuretic.

Salyrgan by its favorable diuretic effect has prolonged lives in many cases of obstinate congestive heart failure and has at the same time made life more endurable. This was true in Case II, recounted above. It is best administered intravenously in a dosage of 1½ to 2 cc. with or without salt solution, great care being taken to avoid the spilling of any of the drug into the tissues around the vein or subcutaneously. If there is a leak of any of the salyrgan subcutaneously considerable pain and tissue destruction with ulceration are likely to occur. Intramuscular injection is safe but sometimes uncomfortable. This method may be used at the outset or in case the veins become thrombosed.

Salyrgan may be given at intervals of a few days or a few weeks as needed. It often is as effective after six months as it is the first day, and it rarely causes toxic symptoms or evidences of renal irritation. The urine should be watched with the latter possibility in mind. The drug is best given early in the morning, for its diuretic effect is most vigorous during the first twelve hours and thus the sleep of the patient is not interfered with. In a few cases where the diuretic effect of salyrgan or mercupurin is unsatisfactory diuretic salts may be given



by mouth for a few days previous to the administration of the mercury to enhance the effect, for example, ammonium chloride 15 grains (1 Gm.) four times a day if tolerated.

Some patients have been given an extraordinary number of injections of salyrgan over periods of a year or two, up to 100 injections or more. Also remarkable diuretic effects are seen occasionally, as much as 6 or 8 liters of urine in twenty-four hours.

Finally, it is important to record the daily fluid intake and urinary output, and if possible to obtain the daily weight of patients receiving salyrgan.

#### PARAVERTEBRAL ALCOHOL INJECTION FOR ANGINA PECTORIS

*Case III.*—H. J., sixty-six years of age, formerly a professional weight lifter, was admitted to the Massachusetts General Hospital for the fifth time on April 29, 1935. His first admission had been ten years previously at which time he complained of typical attacks of angina pectoris of about one year's duration. He had also noticed at that time some dyspnea on effort, nocturnal dyspnea, and swelling of the feet. His past history was irrelevant except for an attack of "rheumatism" at the age of forty-three involving chiefly his ankles, and two eye operations, one for glaucoma, and the other for cataract. Physical examination on his first admission revealed an obese man with extensive arcus senilis in both eyes and fixation and irregularity of the pupil of the left eye from operative procedures. Many teeth were missing. Those remaining were dirty and carious. There was moderate pyorrhea alveolaris. The heart was enlarged to the left, the sounds were of poor quality, and there was a rough apical systolic murmur. The blood pressure was 110 mm. mercury systolic and 50 diastolic. There were a few moist râles at the left lung base. The liver was palpable, 3 cm. below the costal margin and slightly tender.

x-Ray examination of the heart in 1925 showed a well-marked increase in the total transverse diameter chiefly to the left, and a widened tortuous aorta. The electrocardiogram showed sino-auricular bradycardia, rate 48, and intraventricular block with left axis deviation. Examination of the blood was normal. The blood Wassermann reaction was negative. The nonprotein nitrogen of the blood was 35 mg. per 100 cc. of blood. The urine was normal on several occasions.

Following digitalis therapy and the removal of several abscessed teeth he showed moderate improvement and was discharged with a diagnosis of arteriosclerotic heart disease and angina pectoris. He was advised to continue with digitalis,  $1\frac{1}{2}$  grains daily, and to take potassium iodide, 10 drops three times a day.

He moved his place of residence and was not seen again for six years. In September, 1931 he returned complaining of frequent attacks of angina pectoris even when at rest. He was very nervous and reacted severely to his attacks of pain which made them totally incapacitating. The pain, for the most part, radiated to the left shoulder and down the left arm, but occasionally to the right shoulder and arm. On account of the crippling nature of his attacks which did not respond to the usual medical measures, paravertebral alcohol

(95 per cent) injection was advised and carried out by Dr. J. C. White. The first, second, third, and fourth dorsal sympathetic ganglia on the left were injected. Except for pleural pain incident to the injection and intercostal neuralgia for several weeks following the injection there were no complications. He was discharged on the tenth postoperative day considerably improved, having had no substernal pain since the injection was made. The electrocardiogram at this time was essentially as previously described, the heart rate being 60.

Following the left-sided injection he had no further pain over the left precordium nor down the left arm. But as time went on he continued to have substernal oppression with radiation to the right side. This became quite as incapacitating as the pain which had previously radiated to the left side. Along with this were some symptoms and signs of myocardial weakness such as dyspnea on effort and at times a few râles at the lung bases, but never any gross evidence of congestive failure.

In May, 1934, nearly three years after the left-sided alcohol injection he was admitted to the Massachusetts General Hospital again. On account of the continued severity of his symptoms alcohol injection on the right side was considered. However, injection of the first five dorsal sympathetic roots with novocain alone was tried first. This resulted in almost complete relief of pain for a period of about ten weeks following injection and justified a subsequent alcohol injection of the first, second, and third, right dorsal roots which was done a year later (April, 1935). Since that time to the present (December, 1935) he has been much improved. No severe attacks of angina pectoris have occurred and he is able to keep relatively comfortable by using several nitroglycerin tablets daily to control the slight substernal discomfort which he experiences on effort.

**Discussion.**—Paravertebral alcohol injection for the relief of pain due to cardiac or aortic disease has become an established and useful method of treatment, particularly in cases of intractable angina pectoris and large aortic aneurysms. It has developed from the crude early attempts to relieve angina pectoris by cervical sympathectomy which was introduced by Jonnesco<sup>3</sup> in 1916. The development of our knowledge of the anatomy and physiology of the cardiac nerves has resulted in great improvement in the operative attack on angina pectoris. It is now possible to resect the nerves responsible for carrying the pain of angina pectoris to the central nervous system, namely, the first four or five dorsal rami communicantes on either side. Cervical sympathectomy is clearly recognized now as largely ineffective. However, the operation of dorsal sympathectomy is a difficult one and less advisable in most patients with angina pectoris than the much simpler but somewhat less accurate therapeutic measure of paravertebral alcohol injection.

In 1925 Mandl<sup>4</sup> introduced paravertebral novocain injec-

tion which gives temporary relief from angina pectoris. Swetlow,<sup>5</sup> the following year, introduced paravertebral alcohol block of these same dorsal sympathetic rami communicantes. Since that time the technic of paravertebral alcohol injection for angina pectoris and for the pain of aortic aneurysm has been greatly developed by James C. White.<sup>6</sup> In the last 20 cases treated in this way by White there has been no failure to obtain the desired effect.

The procedure is carried out under local anesthesia on the side in which most of the pain of the angina pectoris is located or to which it is referred. This is usually the left side. In occasional cases both sides have been treated in sequence at intervals of days, weeks, or months. Long needles are inserted paravertebrally, usually at the level of the first four dorsal nerve roots. Novocain is then injected and the determination is made forthwith of its effect on the sympathetic nerves (Horner's syndrome, dry warm hand, anesthesia over the left chest). If the proper effects result from the novocain, alcohol is then injected. For details of the procedure see White's recent monograph on the autonomic nervous system.<sup>6</sup>

Aside from the failure to reach the proper sites there may be a few minor hazards concerned, that is, irritation or penetration of the pleura, and intercostal neuritis. Successful cases have shown usually permanent relief from a large part of the pain or distress on the side injected. Usually there remains a warning sensation which keeps the patient's activity under control. This sensation is not pain but a feeling of something wrong.

The patients to be selected for this therapeutic measure are cases of obstinate angina pectoris who are miserable from the constant repetition of angina pectoris even when leading much restricted lives, who have not been helped by medical measures consisting chiefly of rest and vasodilating drugs, and who are not thought to be suitable cases for total thyroidectomy, and also a few cases with severe pain due to the pressure of large aortic aneurysms.

Paravertebral alcohol injection probably has no direct influence on the underlying disease process, namely, coronary atherosclerosis, nor on the duration of life, but it does make

life much more endurable in most patients and it may conceivably even add to the duration of life indirectly by reducing the reaction incident to angina pectoris itself. Very rarely the removal of the disagreeable symptom of angina pectoris has resulted in careless overactivity and the precipitation of a fatal heart attack.

### TOTAL THYROIDECTOMY FOR ANGINA PECTORIS

**Case IV.**—W. G. R., a sixty-seven-year-old physician, was first seen by us on April 7, 1934. He had always been a vigorous worker and well and active except for appendicitis in childhood and a recurrence of this condition at the age of sixty-two, requiring appendectomy. A ventral hernia resulted. In 1922 and in 1928 respectively, each time when very tired, he had a cardiac arrhythmia, probably consisting of premature beats, which was relieved on both occasions by taking a vacation from his busy practice. His blood pressure was said to have been persistently low (90–100 systolic) for a number of years.

In 1932 he first noticed substernal oppression on walking fast after dinner. This symptom recurred infrequently and mildly thereafter whenever he hurried. In November, 1933 the trouble increased sharply in frequency and severity, coming on slight provocation. It was relieved by whisky, but more promptly by nitroglycerin. During February and March, 1934, the pain, which had previously always come on slight or moderate effort, had occurred on six occasions at night while at rest. He was bothered occasionally by palpitation, but there was no dyspnea. His recent treatment had consisted of rest, omission of tobacco, euphyllin, and nitrites when necessary. These measures were not sufficient to control his symptoms. He slept poorly and was upset considerably by the serious illness of a relative.

Physical examination in April, 1934, showed him to be well developed and of large build. He seemed tired and quite nervous. His breathing was normal. The skin was slightly pale. The pupils reacted normally to light and distance. There was no arcus senilis. The thyroid gland was not palpable. The teeth were all out and replaced by dentures. The tonsils were normal in appearance. There was no engorgement or abnormal pulsation of the neck vessels. The apex impulse of the heart was felt in the fifth interspace, 9 cm. from the midsternum in the midclavicular line. There was no abnormal dullness at the base or to the right of the sternum. The heart sounds were of good quality, the rhythm was normal, the rate was 60, and there were no murmurs. The artery walls were soft. The blood pressure was 112 mm. mercury systolic and 70 diastolic. The lungs were clear. The abdomen and extremities were normal.

On fluoroscopic examination the heart was found to be slightly enlarged and the aorta somewhat tortuous. The electrocardiogram showed normal rhythm, rate of 80 and upright T waves in the three classical leads.

A diagnosis of coronary heart disease with angina pectoris was made. Normal activity seemed limited to the extent of 75 per cent by his cardiac condition, and the prognosis was regarded as uncertain. He was advised to rest more completely, to limit his activity according to symptoms, to eat a light reducing diet, to take phenobarbital three times daily, and nitroglycerin when needed. Alcohol injection of the dorsal sympathetic nerves was considered for later use as a palliative procedure.

He improved somewhat on the above régime but not sufficiently to permit him reasonable activity or the resumption of his practice. In June, 1934, he returned for further observation. At this time he was still nervous and impatient to have something more radical done. There had been essentially no change in his physical condition from that previously recorded. The pulse was regular at a rate of 72, the heart showed only slight enlargement, the heart sounds were excellent, there was no edema, and the blood pressure was 125 systolic and 80 diastolic. The basal metabolic rate on three occasions was found to be -11, -15, and -13 per cent respectively.

With the improvement in symptoms the possibility of coronary thrombosis seemed less likely. Therefore, in spite of his age and a rather low metabolic rate, total thyroidectomy was done on June 19, 1934, with the hope of improving the coronary circulation sufficiently for his needs of light activity. He withstood the operation well and went home on the eighth postoperative day.

Two months following the operation he reported that he had had no angina pectoris and was feeling well. The basal metabolic rates at one and two months after operation were -31 and -37 per cent respectively. He looked well except for slight puffiness beneath the eyes. The heart sounds were good, and the blood pressure was 110 systolic and 70 diastolic. He had gained weight. The electrocardiogram showed no change except for slightly lower T waves. At this time he was permitted to resume light work and was given thyroid extract,  $\frac{1}{4}$  grain daily.

His condition has remained satisfactory up to the present time (December, 1935), especially when compared to the relative invalidism he suffered before thyroidectomy was done. He is well except for some coldness of his extremities and a little substernal aching on much walking, or on smoking which he has resumed. He has varied the dose of thyroid extract from  $\frac{1}{4}$  to 1 grain daily. At the higher dosages the metabolic rate is correspondingly higher and substernal oppression is more easily provoked. For more than a year now he has worked steadily in his office and has made unhurried home visits, except for three weeks vacation during the summer of 1935.

The total time elapsed since total thyroidectomy was done has been seventeen months.

**Discussion.**—In 1927 a patient with heart disease and supposed thyrotoxicosis had a subtotal thyroidectomy performed at the Peter Bent Brigham Hospital in Boston and was much improved insofar as the heart condition was concerned for a period after the operation. Histological examination of the thyroid gland of this patient showed no disease. This was the experience behind the idea of thyroidectomy for heart disease. But several years elapsed before this method of treatment was actually instituted by Blumgart and Levine. At first the results were disappointing, the beneficial effects lasting but a brief time. It was then realized that total thyroidectomy, and not subtotal, was essential for the sufficient permanent reduction of the basal metabolic rate and work

of the heart, whereby the heart might recover from its state of fatigue and failure or from its coronary insufficiency. With the help of their surgical associate, Dr. Berlin, Blumgart and Levine then carried out total ablation of the thyroid gland in a series of patients with obstinate angina pectoris or congestive heart failure.<sup>7</sup> In some of these patients there was a striking measure of relief, in others slight benefit, and in still others it was evident that the operation had not been advisable.

Total thyroidectomy in the treatment of obstinate angina pectoris or of recurrent congestive failure has hardly passed through its preliminary experimental phase. Some years more are needed for a completely satisfactory evaluation, but there are, at least, occasional cases still alive today who have been unquestionably benefited. One such case is that recounted above.

The selection of cases for the operation is of prime importance. In the first place the patient should have the full benefit of extensive medical treatment over a period of at least several months before being offered this operative measure. On a number of occasions we have seen patients who had had unsatisfactory response to rest and medication during the course of a few weeks, but who gradually improved with striking degree in the course of the next few months from medical therapy alone. In the second place there are patients in whom the operation is contraindicated. These include cases who are seriously ill with intractable congestive failure or recent coronary thrombosis, or, indeed, angina pectoris decubitus of very high degree. Other contraindications are cardiovascular syphilis, very low metabolic rates (minus 15 or minus 20 per cent or less), very old age (over 70), and the presence of a considerable amount of renal or pulmonary disease. It is also to be distinctly understood that total thyroidectomy does not have any beneficial effect on hypertension or on psychoneurosis which may complicate heart disease and exaggerate its symptoms. This leaves a small group of patients who are suitable for this therapeutic measure, mostly middle aged persons with angina pectoris or congestive failure, completely or almost completely free from symptoms while at rest in bed, but in whom the symptoms recur when up and about.

Total thyroidectomy itself is a major operation demanding very careful preoperative preparation, skilled surgery by an experienced operator, and careful postoperative attention. However, thyroid surgery had developed to such a degree, including its application to seriously ill thyrotoxic cardiac patients, especially by Drs. Lahey and Hamilton, that the stage was already set for this new procedure of total thyroidectomy in the treatment of heart disease. Postoperatively the basal metabolic rate sinks in the course of a few months to a low level, and signs and symptoms of myxedema then begin. At such a time or just before it, say two months after operation, thyroid extract in small dosage, usually  $\frac{1}{4}$  to  $\frac{1}{2}$  grains of Armour's Extract daily, should be instituted to prevent the development of frank myxedema. Moderate hypothyroidism with a basal metabolic rate between minus 20 and minus 30 per cent is, in most cases, the desired effect. It is important for patients to be closely followed and impressed with the need of maintaining this state in which both cardiac symptoms and myxedema are held in abeyance. It seems almost certain that in some cases, at least, life can be not only considerably prolonged, but also made more comfortable by total thyroidectomy. As a radical therapeutic measure, however, it needs to be reserved as therapy of last resort and applied to perhaps 1 or 2 per cent of cases with angina pectoris or congestive failure.

#### CHRONIC CONSTRICTIVE PERICARDITIS

Case V.—B. K., a girl aged ten years, entered the hospital on October 13, 1931, with a history of having lived a semi-invalid life since the age of five and one-half years due to a markedly enlarged abdomen resulting from the presence of much ascitic fluid. When she was twenty months old she suffered from what was apparently an attack of acute pericarditis, and her abdomen became enlarged at that time. At the age of two and one-half years a laparotomy was performed and a gangrenous appendix was removed. No tubercles were seen on the peritoneum at the time of operation. A drain was inserted, and the patient made a good recovery. The fluid returned in about three weeks but following an abdominal tap one month later there was no recurrence of fluid for three years. At the age of five and one-half years the abdominal fluid returned, and six months later a Talma operation (omentopexy) was done. Abdominal fluid injected into a guinea-pig gave negative results. There was no improvement following this operation, and at the age of nine the patient entered a second hospital for further study. Her abdomen was tapped at that time, but not again after that until her entrance into the Massachusetts General Hospital in the fall of 1931 when 6240 cc. of straw-colored fluid with a specific gravity of 1.013 were removed.

Her mother had died of tuberculosis during the patient's infancy. Her father is living and well.

Physical examination showed a thin, somewhat pale, young girl with heart apparently normal in size and sounds and without murmurs, and with prominent jugular veins and a large protuberant, nontender abdomen, filled with fluid (Fig. 167). x-Ray examination showed the heart and great vessels somewhat displaced to the right and anchored to the diaphragm; no pulsation was evident at the right border of the heart and great vessel shadow; the right pleura was thickened.

The electrocardiogram showed normal rhythm, rate 100, with inverted T waves in Lead 2 (Fig. 169, A).

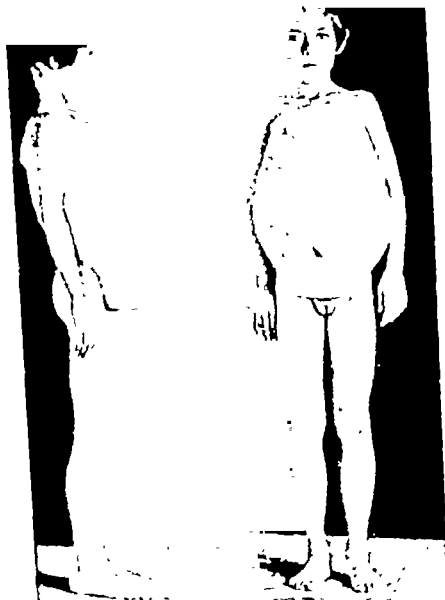


Fig. 167 - Case V at the time of her disability. Her condition was unchanged for seven years (five to twelve years of age).

Advice was given at that time that the chest be explored surgically and the adhesions constricting the right auricle, right ventricle, and great veins be freed.

After an interval of two years this girl returned to the hospital in an unchanged condition with persistence of the enlargement of the abdomen. The serum protein measured 4.3 per cent. x-Ray and electrocardiographic findings were as before.

Pericardial resection was carried out on November 16, 1933, and a moderately thickened pericardium containing calcareous plaques was removed from over the right ventricle and right auricle by Dr. Churchill. The pericardial tissue that was removed showed fibrosis and calcification on examination. There was a stormy time for two days after the operation. Finally spon-



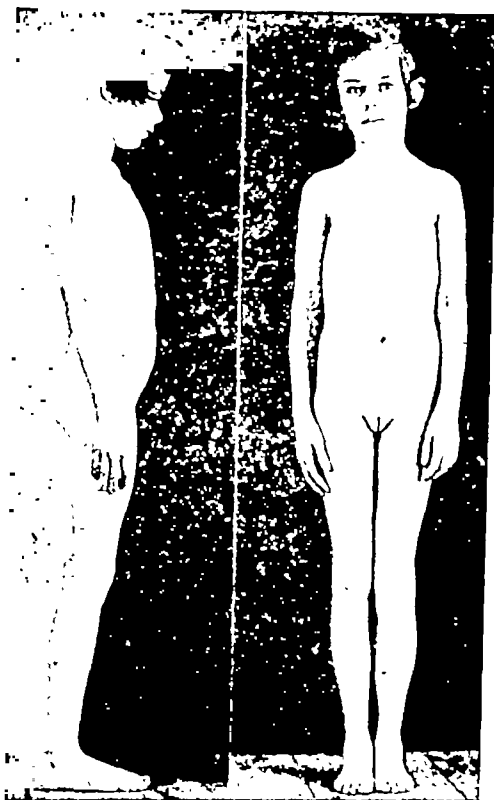


Fig. 168.—Case V one year and a half after operation. Her cure was completely effected within a few months of the pericardial resection.

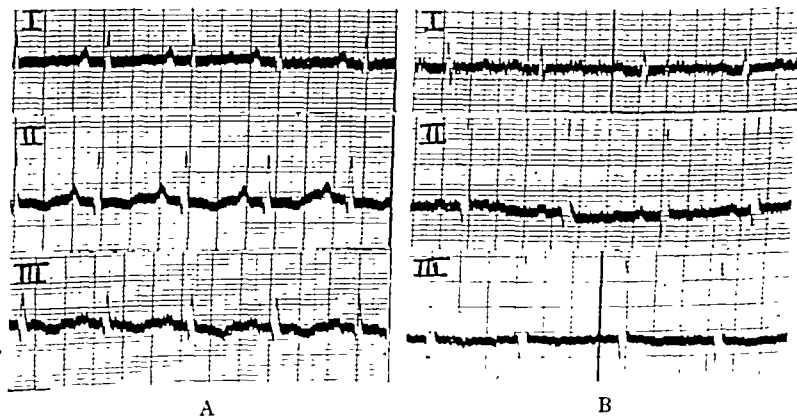


Fig. 169.—Case V.

taneous diuresis began and in the course of a few months the ascites completely disappeared. She has been in excellent health since, and looked well when she was last examined by us on May 16, 1935 (Fig. 168).

The electrocardiogram on May 16, 1935 showed normal rhythm at a heart rate of 80, with slightly upright T waves in Lead 1, flat T waves in Lead 2, and very slightly inverted T waves in Lead 3; this record differed from that taken before the operation in that the T waves were more normal and the voltage of the QRS waves was greater (Fig. 169, B).

**Discussion.**—Chronic constrictive pericarditis or Pick's disease, recognized by only a few medical observers over a period of several hundred years prior to the last decade, is at last amenable to treatment. Formerly a hopeless disease treated by palliative measures to relieve dropsy, consisting chiefly of rest, restriction of fluid and salt intake, abdominal paracentesis and diuretics, it now yields to surgery in a considerable percentage of cases.

In 1895 Delorme of Paris tried to persuade the surgeons of his hospital to undertake to free the heart from its constricting pericardial adhesions. After three years of failure in his attempt to interest them, Delorme,<sup>8</sup> in 1898, announced his ideas to the medical world in an open meeting in Paris, several years before Brauer<sup>9</sup> offered his much less important plan of freeing the heart (rib resection and cutting of external adhesions). It is strange that Brauer's operation became much better known than the more vital pericardial resection advocated by Delorme. Finally, in 1913, Sauerbruch and Rehn independently carried out Delorme's suggestion. During the next ten years a few cases were operated upon in Germany, but it has been only in the last decade that pericardial resection has been firmly established as a cure for chronic constrictive pericarditis.

It is important in the first place to establish the diagnosis of chronic constrictive pericarditis. Following an infection which is often obscure but involves the pericardium and at times the pleurae and peritoneum (polyserositis), the pericardium becomes thickened, callous, constricted, and sometimes calcified. The cause of the original acute pericarditis is often unknown. In a few cases it is definitely tuberculous, in others it is associated with pneumonia and pleuritis; in a few it is septic in nature (when there is survival), but it seems never to be rheumatic. As noted by one of us in a recent

paper<sup>10</sup> on chronic constrictive pericarditis, "The leading clues are the result of inflow stasis, namely, (1) the insidious onset of dropsy in a young person, (2) preponderant liver enlargement and ascites, (3) increased prominence of the jugular veins, (4) normal or relatively normal heart in the presence of dropsy without nephritis, and (5) low blood and pulse pressure and paradoxical pulse. Other important clues are (6) x-ray evidence (poor pulsation, calcification, chronic pleuritis), (7) electrocardiographic abnormalities (low voltage or coronary T waves in chronic disease in early youth), and (8) previous history of acute pericarditis or polyserositis." The three conditions most commonly confused with chronic constrictive pericarditis are rheumatic heart disease with mitral stenosis and congestive failure, primary cirrhosis of the liver, and polyserositis including instances of perihepatitis or frosted liver.

The operation itself, done under general anesthesia, preferably ether, is a difficult one and to be trusted only to a skilled thoracic surgeon. About an hour is needed for the approach to the chief operative field, namely, the pericardium itself. Three or four rib ends and costal cartilages, usually the fourth, fifth and sixth, and the left edge of the sternum are removed. The pleurae are carefully retracted, the pericardium incised and both parietal and visceral layers, usually adherent to each other and as thick as shoe leather, are carefully dissected off from the surface of the heart, most commonly from the right ventricle and right auricle. This procedure takes about another hour, and, if successful, the heart obviously expands during the course of the operation while it is being freed from the constricting pericardium, the pulse improves and the pulse pressure increases. Recovery may be rapid or slow following the operation. Sometimes a spontaneous diuresis develops during the course of the very first week postoperatively and in two or three weeks the congestion may entirely disappear, resulting in an early cure. In other cases progress is much slower and several months may elapse before there is marked improvement or cure. In a few cases operation may be unsuccessful and in another few it may cause an early fatality. In our own series of 12 cases of pericardial resection done at the Massachusetts General Hospital by one surgeon (Dr. E. D.

Churchill) there have been six cures, two other recent cases apparently on the way to a cure or high degree of improvement, and one other case more than 50 per cent improved. Thus, although this disease is rather rare, it is now of vital importance that it be recognized and its victims offered this new opportunity for cure. The history recounted above is one of our successful cases.

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### RECENT ADVANCES IN THE TREATMENT OF ARTERIAL HYPERTENSION

#### SYNOPSIS

- I. General Consideration of Therapeutic Measures.
- II. Chemical Substances:
  - The nitrites.
  - The alkyl nitrates.
  - Bismuth subnitrate.
  - Tissue extracts.
  - Histamine.
  - Acetylcholine.
  - Acetyl- $\beta$ -methylcholine.
  - Adenosine and adenylic acid.
  - Cucurbitacin.
  - Potassium thiocyanate.
  - Ovarian hormones.
- III Dietary Measures.
- IV Surgical Measures:
  - Procedures to influence the hormonal production of the glands of internal secretion.
  - Section of the splanchnic nerves.
  - Direct denervation of the suprarenal glands.
  - Suprarenalectomy.
  - Operations for the purpose of influencing nerve impulses of the vasomotor system.
  - Denervation of the kidneys.
  - Section of the splanchnic nerves.
  - Spinal nerve root resections.
  - Combined surgical measures.
  - Critique of the surgical treatment of arterial hypertension.
- V Conclusion.
- VI Bibliography.

DEVIATIONS from the normal level of arterial pressure are often responsible for clinical symptoms and frequently lead to disturbances of bodily functions. While the prognosis in arterial hypotension is good as far as structural disturbances and longevity are concerned, the serious cardiac, neurologic, renal and other organic complications of chronic arterial hypertension are well recognized. In the prevention of these secondary vascular disturbances and "organ insufficiencies," adequate treatment of "uncomplicated" hypertension is essential. The following discussion will be restricted to an evaluation of attempts recently undertaken for the treatment of "uncomplicated" arterial hypertension.

#### I. GENERAL CONSIDERATION OF THERAPEUTIC MEASURES

Efforts to abolish arterial hypertension effectively have so far been uniformly characterized by failure. This is not surprising when one considers that in spite of significant evidence indicating that hypertension is the result of mechanisms of varied etiology, the details of these mechanisms are little understood.<sup>1</sup> As a result, no successful therapy directed against etiologic factors exists, nor can it be rationally devised at present. All one can attempt to do is to search for measures which tend to reestablish the normal level of the arterial pressure with the maintenance of adequate capillary blood flow through the tissues both at rest and during physiologic activities of the body. This latter consideration is particularly important, for although one can lower the blood pressure with relative ease in a number of ways, there is usually ultimate damage to the organs.

There are a number of facts now firmly established, the knowledge and proper evaluation of which are essential in the effective treatment of hypertension. In the majority of instances of arterial hypertension, in which both the systolic and the diastolic pressures are considerably elevated and the pulse pressure is usually high, the primary and most significant change consists in an increase in the "tonus" of the arteriolar as well as of the arterial walls.<sup>2, 3</sup> The relative degree of involvement of the arteriolar and arterial systems, respectively, varies in different types of hypertension. The chief factor is usually the increased tonus of the arteriolar rather than of the

arterial system, which in turn causes a notable increase in the resistance of the vascular tree to the blood flow. The pressure within the capillaries, as judged from the behavior of the cutaneous capillaries and of the spinal fluid pressure, is usually but not necessarily, normal. Similarly, the systemic venous pressure and the pressure relations within the pulmonary circuit are, in the majority of uncomplicated cases, within the limits of normal. The circulating blood volume and the viscosity of the blood are also normal. Since the cardiac output, the stroke volume of the heart, and the maximal and mean velocities of the circulation are likewise normal, it follows that the mean supply of blood to the tissues is the same in patients with hypertension as it is in normal subjects.<sup>3, 4, 5</sup> These findings, now confirmed, clearly indicate also that the increase in arteriolar resistance is diffuse throughout the body. That such is actually the state of affairs in the skin and in the striated muscle tissues is shown by direct observations recently made in this laboratory.<sup>6, 7</sup> That in some of the organs ischemia and hyperemia may exist simultaneously as a result of a relatively increased constriction or relaxation of the arterioles is possible, and from certain observations is even probable.<sup>8</sup> This does not, however, alter the fundamental fact that in spite of change in the physical properties (changes in tonus) of the arterioles and of the arteries a remarkable homeostatic regulation exists in hypertension which results in an adequate and normal supply of blood to the tissues at rest and under physiologic stimuli. This homeostatic adjustment is accomplished by increased work on the part of the heart and by increased arterial and arteriolar pressure on the part of the circulation. It is important to reemphasize that the circulatory adjustments in hypertension are performed with good economy, and that *there is no overabundance of blood supply to the organs in hypertension*. Such considerations inevitably lead to the conclusion that *arterial hypertension is primarily a progressive obstructive disease of the arteriolar system and a progressive alteration of certain physical properties of the arterial system*. The elevations of the diastolic and systolic pressures are secondary manifestations, and they must be looked upon as compensatory adjustments for the maintenance of adequate capillary circulation in the tissues.



The exact *nature of the change* in the arterioles and arteries is unknown. At the present time all that we know is that the increase in "tonus" can be either reversible, or partially or completely fixed. It has been assumed from indirect clinical evidence that the source of the increased tonus, particularly in the early stage of hypertension, is increased efferent sympathetic nervous impulses in the vasomotor system. Actually, clinical experimental attempts to demonstrate such striking difference in the tonus of the autonomic nervous system in patients with arterial hypertension as compared with that in control subjects have thus far failed.<sup>7, 9</sup> Practically all the increased vascular responses observed in hypertension, which have been claimed to result from increased sympathetic impulses, can be explained as due to increased irritability of the vessels themselves. Our knowledge is therefore in a paradoxical state; namely, in spite of the fact that we can demonstrate changes in the tonus of the arterioles and arteries, we cannot demonstrate the increased sympathetic impulses, nor can we identify circulating chemical substances leading to increased tonus.<sup>10</sup>

This consideration of the mechanism of arterial hypertension is helpful in defining those characteristics which therapeutic measures must possess in order to be beneficial in hypertension. An effective measure must obviously decrease arteriolar and arterial tonus and resistance without essentially disturbing other fundamental characteristics of the circulation, such as the cardiac output, the velocity of blood flow or the volume of circulating blood. The measure must maintain normal and adequate blood flow to the organs, particularly to the heart, brain and kidneys, at rest and in times of physiologic stress. The effect of the measure must be such that sudden drops in the blood pressure are avoided, and if possible the spontaneous fluctuations present in hypertension toned down. Establishment of a permanent lower level should occur gradually. The vasomotor responses essential to normal bodily functions should not be affected.

Let us ascertain whether the measures introduced fulfill the rationale of these requirements.

## II. CHEMICAL SUBSTANCES

**The Nitrites.**—The vasodilator properties of this group of substances have been known for a long time. It is only in late years, however, that the rationale of their use in arterial hypertension and in angiospastic disorders has been examined critically. Recently it has even been claimed that minute amounts of nitrites are normal constituents of the human blood.<sup>11</sup> The nitrites act chiefly, if not entirely, on the peripheral vascular system and produce vasodilatation, probably as the result of direct action on the smooth muscles of the vessel walls. The site of their activity is chiefly the arterial side of the vascular bed. The depressor effect is greater on the systolic than on the diastolic pressure. The comparative stability of the diastolic pressure suggests that the dilator effect of the nitrites on the small arteries and arterioles is neither constant nor marked. As far as the cardiac output is concerned, it either remains normal or becomes reduced. Similarly, the kidney function remains unaltered or becomes reduced as the result of the changes in the cardiovascular system.<sup>12</sup> These changes suggest that in some respects the nitrites are suitable agents for reducing arterial pressure. Their greatest drawback is their fleeting action. Moreover, in effective doses they may temporarily impair kidney function, and with the patient in the erect position they may cause increased strain on the circulation and at times fainting. The effects of sodium nitrite last but one or two hours, and some of the related compounds, such as amyl nitrite, have an action of much shorter duration, which can be measured in terms of minutes. Recently attempts have been made to use compounds that are absorbed slowly from the gastro-intestinal canal, such as bismuth subnitrite, in order to insure a longer persistence of action. So far, however, such efforts have not proved successful. The short duration of action of the nitrites results in a constant and abrupt fluctuation of the arterial pressure, which in turn precipitates symptoms, and therefore their continued use may even become dangerous, particularly in patients with arteriosclerotic changes. In view of these considerations, the main use of the nitrites is in acute vasospastic states, such as occur in vascular crises.

**The Alkyl Nitrates.**—The principal representatives of

this group, glycerol trinitrate, erythrol tetranitrate and mannitol hexanitrate, can induce marked reduction in the arterial tonus, particularly if the latter is increased. The duration of effect of this group of substances is again relatively short, though erythrol tetranitrate may lower the blood pressure for from two to three hours, and mannitol hexanitrate for as long as four or five hours. As far as the maximum depression of the blood pressure is concerned, 1 mg. ( $\frac{1}{100}$  grain) of glycerol trinitrate is equivalent to about 30 mg. ( $\frac{1}{2}$  grain) of erythrol tetranitrate or to 60 mg. (1 grain) of mannitol hexanitrate by mouth. It takes from twenty to thirty minutes for the last two substances to exert their action after oral administration.

For the same reasons as apply to the nitrites, the routine use of alkyl nitrates in arterial hypertension is not feasible; furthermore they are too expensive. Their main indication is in acute vasopastic states, such as occur in vascular crises and in angina pectoris.

**Bismuth Subnitrate.**—The beneficial effect of this substance has been reported by Stieglitz.<sup>13</sup> It has been claimed that mild relaxation of the arterial system follows the oral administration of doses of 0.6 Gm. (10 grains) three times daily. Since this salt is relatively insoluble, there is a continuous liberation of minute amounts of nitrate within the intestines. It is claimed that under the influence of the colon bacillus the liberated nitrate ions are reduced to nitrites. Stieglitz and Palmer offered evidence to show that following the administration of bismuth subnitrate the nitrite concentration of the blood increases.<sup>14</sup> Such medication serves a double purpose, according to Stieglitz. It reduces the arterial pressure and relaxes the arterioles, thereby breaking "the vicious circle of arteriolar fatigue." According to the experience of Stieglitz, a demonstrable reduction in the arterial pressure occurred in 77 per cent of the patients.<sup>13</sup> The maximal reduction may be reached only after weeks of using the drug. Since the medication is certainly harmless and at the same time is inexpensive, it deserves trial as a symptomatic remedy, although in routine clinical use one has difficulty in seeing its benefit. Several reports in the literature also deny its therapeutic value.

**Tissue Extracts.**—During the past few years renewed claims have been made that extracts of muscle, liver, heart,

pancreas, brain, kidney and spleen exert a beneficial influence in arterial hypertension and in other vascular disorders, particularly angina pectoris. Such extracts, under the trade names of "myol," "lacarnol," "myoston," "padutin," "hormon kardiol" and others, are extensively used in Europe and America. That tissue extracts can reduce the arterial pressure in experimental animals has been known for a long time. The active factors were thought to be vasodilator substances. The recent claim, however, is that the alleged beneficial effect of these substances depends on circulatory hormones and only secondarily on vasodilator substances. For the existence and the nature of such circulatory hormones little and rather poor evidence is found in the literature; it is questionable, therefore, whether any greater benefit can be attributed to these preparations than to the combination of vasodilator substances contained in tissue extracts. These substances include histamine, choline and adenosine or adenylic acid and their derivatives. The cardiovascular effect of other substances present in tissues is negligible. Until we attain greater understanding of the effect of these substances on the vascular system, the clinical application of tissue extracts containing variable concentrations of vasodilator substances must be considered as empirical and unsettled.

**Histamine** is often considered as a potent vasodilator substance, and in certain species of animals, under experimental conditions, such is the case. It has been shown, however, that normal subjects given an intravenous infusion of histamine up to toxic doses continuously for two hours fail to respond with an appreciable lowering of the arterial blood pressure.<sup>15</sup> In some instances the diastolic pressure shows a tendency to fall, but in numerous instances it remains unaltered. As judged from the behavior of the hemodynamics and from the vascular responses, arteriolar dilatation develops only in certain organs, and is associated with such changes in the heart and other organs as to make the therapeutic application of this or related substances as vasodilators questionable. It is of especial interest that when observations similar to those conducted on normal subjects were made on a group of patients with arterial hypertension, the response was similar in every respect to that observed in normal subjects. From the same concen-

tration of histamine the degree of elevation of the skin temperature was the same in normal subjects as in patients with arterial hypertension. This indicates that the degree of relaxation of the cutaneous arterioles was actually less in the hypertensive than in the normal subjects, but that the degree of increase in blood flow was the same in both groups.<sup>16</sup> This constitutes additional evidence that in arterial hypertension the arteriolar responses to physiologic and other stimuli are such that the resulting blood flow is within the limits of normal.

These findings, together with its fleeting action and the fact that it is entirely ineffective even in massive oral doses, make histamine entirely unsuited for use in the treatment of arterial hypertension.

**Acetylcholine.**—The work of Dale and his associates<sup>17</sup> has amply demonstrated that choline, a derivative of lecithin, and its esters represent the most potent vasodilator constituents of tissue extracts. Recently it has also been claimed that some of the choline compounds play an important rôle as chemical mediators of nerve impulses on cells with motor activities. It has also been proposed that choline acts as a regulator of intestinal peristalsis and tone. It is a remarkable pharmacologic fact that by the introduction of an acetyl radical the physiologic potency of choline in reducing arterial pressure increases one hundred thousand times, and such a minute amount as 1 cc. of a 1: 100,000,000 dilution of acetylcholine produces a fall in the blood pressure of the rabbit of 20 to 25 mm. Hg. It was natural, therefore, to expect that a substance with such biologic properties might be a suitable agent for the treatment of arterial hypertension. As a result of such claims by French clinicians, acetylcholine (under the trade name of "acecoline") came into use as a vasodilator.

The following consideration of the action of acetylcholine in man reveals at once that its therapeutic applicability as a vasodilator is limited. First of all, it has been demonstrated that man is relatively tolerant to this substance.<sup>18</sup> After oral administration of even massive doses no systemic effects are noted. Even when as large a dose as 1 Gm. (15 grains) is infused evenly intravenously within a period of ten minutes, and mild toxic manifestations are precipitated, the arterial pressure either remains normal or is only slightly reduced. A

moderate degree of arteriolar dilatation develops, but circulatory adjustments apparently compensate for the dilatation in such a manner that the blood pressure does not change significantly. Furthermore, the effect is only transient, owing to the fact that acetylcholine is promptly destroyed within the blood stream. The effect of intramuscular administration of acetylcholine is unreliable and variable. In the few instances in which we have observed the effect of acetylcholine in patients with arterial hypertension we have found the response of the cardiovascular system similar in every respect to that in normal subjects.

These considerations, together with the expense, clearly demonstrate that acetylcholine is not a suitable substance for routine use in arterial hypertension. In certain acute vasospastic states, on the other hand, it may be useful when it is administered intravenously with proper understanding of its pharmacologic and toxicologic qualities.

**Acetyl- $\beta$ -Methylcholine.**—This substance, like acetylcholine, produces vasodilatation and a certain type of parasympathetic stimulation.<sup>19</sup> When given intravenously to anesthetized animals, the vasodilator effect of the two compounds is of the same order of magnitude, but the action of acetyl- $\beta$ -methylcholine ("mecholin") is of longer duration owing, presumably, to its slower hydrolysis in the blood. Following subcutaneous injection, acetyl- $\beta$ -methylcholine is more effective than acetylcholine. The general as well as the cardiovascular responses in normal human subjects following the continuous intravenous infusion of acetylcholine and acetyl- $\beta$ -methylcholine are similar, but the latter substance is approximately two hundred times as potent as the former.<sup>20</sup> The duration of action of these compounds is very short. In man, mild systemic responses can be induced following oral administration of acetyl- $\beta$ -methylcholine. These facts indicate that for parasympathetic stimulation and in acute vasospastic states acetyl- $\beta$ -methylcholine offers advantages over acetylcholine. The effective subcutaneous or intramuscular dose varies from one individual to another, and may be from 5 to 30 mg. ( $\frac{1}{12}$  to  $\frac{1}{2}$  grain).

**Adenosine and Adenylic Acid.**—These and related compounds are, like histamine and choline, natural constituents of

the human body and active principles of organ extracts. Adenosine is formed with ease by the hydrolysis of nucleic acid. Adenosine and adenylic acid are practically identical in their pharmacologic effects, which depend on the ease with which they are deaminized in the body.<sup>21</sup> They act primarily on the heart, and, to a lesser extent, as dilators, on the vessels, including the coronary arteries. Effective doses produce slowing of the heart and disturbances in the intracardiac conduction, leading to block. In tachycardias, including auricular fibrillation, they may induce slowing. In man, intravenous injection of 0.2 to 3 cc. of a watery solution causes sweating, a sensation of warmth, tremor, and restlessness associated at first with tachycardia and later with bradycardia.<sup>22</sup> The T waves of the electrocardiogram may become flat, and delay in conduction may develop.

The evidence for the beneficial effect of these compounds in disease is meager. The combined effect of the cardiac slowing, disturbances of cardiac conduction, vasodilatation and fall in blood pressure which they produce is such that the function of the heart and the state of the circulation are usually not improved, and at times are even made worse. In view of this fact and also in view of the fact that their action is only transient, the therapeutic use of these compounds is undesirable.

The pharmacologic and therapeutic effects of histamine, choline, and adenosine and its related compounds cast *serious doubt on the claims as to the benefit of tissue extracts in hypertension* and in certain other vascular disorders. At best they produce only a fleeting effect, and when administered orally they must be practically inert.

**Cucurbocitrin.**—Extracts of watermelon seed contain glucosides and saponins, which, according to Barksdale, produce a lowering of the arterial pressure as a result of peripheral dilatation.<sup>23</sup> It is claimed that this depressor effect is also obtained after oral administration. No ill effects have been observed. This compound, under the name of "citrin," has so far not proved a particularly useful agent. No further report on its therapeutic use has appeared recently.

**Potassium Thiocyanate.**—Ever since Pauli's claim in 1903 that thiocyanate was effective in reducing high blood pressure, the use of this drug has been advocated from time to

time. Its toxic properties have not been sufficiently appreciated, however, in spite of the fact that they were emphasized by Claude Bernard in 1857. The therapeutic dose should not exceed 1 Gm. (15 grains) per day, and even after such a dose toxic reactions may occur. After larger doses, muscular weakness, psychosis, dermatitis, cardiac pain and fatalities occur. Impaired renal function apparently increases toxicity. Some persons show susceptibility to the drug. The margin of safety between the blood pressure reducing and the toxic doses is narrow. The detailed mechanism of its action has not been investigated as yet. As judged from recent reports, the indiscriminate use of thiocyanate is dangerous.

**Ovarian Hormones.**—It is claimed, especially by German writers, that certain extracts of the ovarian hormones, particularly follicular hormones, lower the pressure and alleviate the symptoms in hypertension. That progynon, administered orally in doses of 1800 units daily, is capable of abolishing the hot flashes of menopause is known. This is the more interesting because, in spite of the fact that in menopause there is underproduction of estrin and overproduction of prolan A, the hot flashes cannot be directly related to the low estrin content or to the high prolan A production.<sup>24</sup> We have pointed out before that the symptoms of uncomplicated menopause, of hypertension appearing during menopause, and of uncomplicated hypertension are essentially identical.<sup>25</sup> Hence estrin may well exert a beneficial effect on the symptoms of hypertension. Whether such therapy influences the level of the arterial pressure has not been established. In 2 cases followed by Albright such hypertension remained unchanged.<sup>26</sup>

### III. DIETARY MEASURES

In recent years the most important advance in the dietary treatment of high blood pressure consists in the correction of dietary restrictions and fads advocated in the past. There now exists adequate evidence that primary hypertension is not associated with metabolic disturbances, and that the kidney function remains good or fair in the majority of instances. In the Boston City Hospital about 10 per cent of the cases with nephrosclerosis die from uremia. It is doubtful whether in



this 10 per cent early protein or salt restriction would essentially have altered the outcome. Hence low protein and intensely restricted salt diets have been abandoned. In view of the chronicity of the condition, such diets often result in deficiency states and precipitate secondary complications. The only significant fact related to diet which we have learned is that in cases of overweight a balanced low caloric diet, which will result in weight reduction, will also result in effective and permanent lowering of the blood pressure. Reduced weight, in addition, lessens the work of the heart. Thyroid extract, dinitrophenol or other reducing agents should not be used, for they may precipitate cardiac disturbances. It is obvious that condiments and an excess of salt should be avoided. It is perhaps rational to encourage a moderately increased water intake, but no reliable evidence has yet been furnished that natural or artificial mineral waters have any specific beneficial effect. Alcohol in minute amounts is a natural compound of the body and burns with ease. Its excessive use is especially harmful to hypertensive patients; its moderate use, particularly in the form of beer or wine, is actually beneficial as a mild relaxer, sedative and vasodilator. In acute vasospastic states it has a distinctly beneficial effect.

#### IV. SURGICAL MEASURES

In recent years vigorous attempts have been made to influence hypertension permanently through surgical measures. In view of the fact that the primary disturbance in arterial hypertension consists in reversible alterations in the physical properties of the arteriolar and arterial systems, and in view also of the fact that during the past decade neurosurgery has made important contributions in the treatment of certain peripheral vascular disorders, it is natural that such attempts should be made. On the other hand, it is particularly important that physicians should realize that the value of these measures is far from being established, and that they must be considered as empirical rather than as based on a rational knowledge of the etiology or, for that matter, even of the mechanism of hypertension.

The surgical measures which have been advocated may be divided into two main groups: (a) procedures devised to

influence the hormonal production of the glands of internal secretion, and (b) operations for the purpose of influencing nerve impulses of the vasomotor system.

#### PROCEDURES TO INFLUENCE THE HORMONAL PRODUCTION OF THE GLANDS OF INTERNAL SECRETION

Of the glands of internal secretion the pituitary, thyroid, adrenal and ovarian glands have been regarded as being responsible for the development of arterial hypertension. There is little basis for such claims, the most tangible evidence so far presented being the claim of Cushing<sup>27</sup> and others that *basophilic adenoma or basophilic infiltration of the anterior lobe of the pituitary* is associated with hypertension. The significance of basophilic infiltration of pituitary cells in relation to hypertension, however, is not settled, and we lack adequate controls. Thus recently Ahlström<sup>28</sup> has denied the existence of a direct relationship between basophilic infiltration and hypertension. Patients with hypertension frequently have no basophilic infiltration and, contrariwise, patients with basophilic infiltration may have normal blood pressure. He quotes Spark, who also failed to find a relationship between basophilism and hypertension.\* So far, perhaps fortunately, nobody has devised surgical procedures to influence pituitary secretion as a measure in the treatment of arterial hypertension. Reports on attempts to irradiate the pituitary gland with x-rays are beginning to appear in the literature, but no convincing evidence as to the benefit of this procedure has yet been presented. Moreover, it is not clear whether such a measure is harmless.

There are two arguments that may be brought forward in favor of the *suprarenal origin of hypertension*: (1) that an overproduction of adrenalin is responsible for hypertension; (2) that an unusual sensitivity to a normal secretion of the gland exists. With the exception of the rare cases of medullary tumors of the adrenal associated with the paroxysmal type of hypertension, there is no direct or indirect evidence

\* Since this paper was sent in for publication a report by Scriba has appeared (Die basophilen Zellen des Hypophysenhinterlappens und ihre Beziehungen zum Hochdruck und zur Eklampsie, Klin. Wchnschr., 14: 1589, 1935). He also failed to find a causal relationship between basophilic infiltration and hypertension.

supporting the contention that circulating adrenalin is responsible for arterial hypertension. *The hemodynamics and behavior of the patient with arterial hypertension differ essentially from those observed in animals or in man during experimentally induced hyperadrenalism.* We have observed that histamine, which in several respects is an antagonist of adrenalin, exerts no influence on any type of hypertension. It is also significant in this connection that complete ablation of the thyroid gland apparently fails to influence the course of arterial hypertension. It is well known that thyroid secretion exerts a sensitizing effect on the action of adrenalin on the cardiovascular system. One would therefore expect that if hyperadrenalinemia, or increased sensitivity of the blood vessels to normal adrenalinemia existed, a change in the hypertension would follow the complete elimination of thyroid secretion.

In spite of these basic considerations, surgical attempts to influence suprarenal secretion have been made and beneficial results have been claimed. Three types of operation have been performed for this purpose: (1) unilateral or bilateral section of the splanchnic nerves; (2) direct denervation of the suprarenal glands; (3) various degrees of suprarenalectomy.

**Section of the Splanchnic Nerves.**—This operation was suggested as a therapeutic procedure in arterial hypertension by Danielopolu as early as 1923. In 1923 Pende<sup>20</sup> advised section of the left splanchnic nerves for the production of vasodilatation within a large abdominal area and for the inhibition of adrenal secretion. Pieri<sup>30</sup> in 1932 resected both splanchnic nerves in 5 cases of essential hypertension. Craig and Brown<sup>31</sup> performed unilateral or bilateral resection of the splanchnic nerves and removed the first lumbar ganglion in 5 cases. They claimed that the operation is relatively safe. In only one of their patients was the subjective and objective improvement striking; in two the only change was the reduction in the pressure reactions to cold, and in the remaining two with early renal involvement and advanced organic changes in the arterioles no benefit was noted. Craig and Brown recognize the fact that removal of the sympathetic nerves does not materially alter the arterial pressure. They think that resections influence the "response" or vasopressor reactions in hypertension. Excessive reactions, it is claimed, cause abnormal

wear and tear on the vascular system. The purpose of the surgical measure is to block or modify these excessive responses before the onset of organic or irreversible lesions. Patients with the "spastic" or "vasomotor" types of hypertension are therefore the most suitable subjects for operation. In a recent communication to me<sup>32</sup> Dr. Brown states that in his opinion, however, the results with subdiaphragmatic bilateral resection are "rather equivocal and not at all dramatic."

Peet<sup>33</sup> has performed bilateral splanchnic nerve section on over 60 patients, all of whom had a systolic blood pressure of 200 or over. His intention was (1) to diminish peripheral blood volume through splanchnic dilatation; (2) to diminish adrenal secretion, and (3) to abolish abnormal vasoconstrictor effects of kidney origin, provided sclerotic changes in the kidney were not too advanced. He also claims that it is conceivable that after removing the elements of spasm and the strain of hypertension, the vessels "might" return to normal. He believes that in 6 cases in which complete relief was obtained such a process accounted for the return of normal kidney function. He confesses that no criterion as to the operability has yet been found. Marked fundus changes and evidence of greatly impaired kidney function are not contraindications. In a recent personal communication Dr. Peet<sup>34</sup> states: "We are continuing to do splanchnic operations for hypertension and believe our results are, on the whole, superior to those obtained by any other of the various surgical procedures. The operation, as developed by us, consists of a superdiaphragmatic approach with resection of the greater and lesser splanchnic nerves and of the lower dorsal sympathetic chain, including 10, 11 and 12 dorsal ganglions. We have always performed the operation bilaterally. Sixty-two per cent of our patients who have gone at least four months after operation showed very definite improvement and a considerably higher percentage have had relief of symptoms. About 15 per cent are cured so far as any evidence of hypertension is concerned. These have all gone at least six months and have maintained normal blood pressure while actively engaged in their former occupations, and have had a complete disappearance of all eye and kidney findings. We have operated over 100 patients. The longest has been followed two years and is maintaining a nor-

mal pressure, normal vision, and normal kidney findings. Before operation he had a blood pressure ranging from 240 to 280 over 180 diastolic. He had choked discs and markedly impaired renal function."

**Direct Denervation of the Suprarenal Glands.**—This procedure was devised by Crile<sup>35</sup> for the relief of symptoms of neurocirculatory asthenia. Others<sup>36</sup> have observed indifferent results following the same operation. It is said that this technic is now practiced in some clinics for the relief of hypertension. Recently, Rogoff\* has reported the occurrence of "Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus." He warns: "The course and outcome in this case strongly support the contention, repeatedly made by me since 1918, that surgical intervention with the adrenals for various conditions (Raynaud's disease, spontaneous gangrene, hypertension, epilepsy, gastric ulcer, thyroid disease, diabetes, and the like) is to be deprecated. The very fact that it is alleged to be of benefit in so great a variety of diseases ought to render the practice suspect."

**Suprarenalectomy.**—The experiences of Galatà,<sup>37</sup> of Monier-Vinard, and Desmarest<sup>38</sup> and of Pieri<sup>39</sup> with unilateral suprarenalectomy do not reveal any benefit following operation. The blood pressure became lowered for only a short period, and obviously this was the result of surgical trauma. The surgical removal of pheochrome tumors of the suprarenal, on the other hand, has resulted in marked benefit to the patient.<sup>39</sup>

DeCourcy, DeCourcy and Thuss,<sup>30</sup> believing "that the most rational method of treatment of essential hypertension is the surgical excision of sufficient amounts of glandular tissue to relieve the excessive functioning of the gland itself," removed about two-thirds of each suprarenal gland, including both medulla and cortex. They claim benefit in some of the patients as far as symptoms and lowering of the blood pressure are concerned. From their presentation it is difficult to judge the extent of the control observations.

\* Jour. Amer. Med. Assoc., 106: 279, 1936.

OPERATIONS FOR THE PURPOSE OF INFLUENCING NERVE IMPULSES OF  
THE VASOMOTOR SYSTEM

These procedures may be grouped into the following main groups: (1) surgical denervation of the kidneys; (2) splanchnic resections; (3) anterior spinal nerve root resections; (4) combination of these procedures.

**Denervation of the Kidneys.**—This procedure was carried out recently by Page and Heuer<sup>40, 41</sup> both in patients suffering from severe essential hypertension and in patients with chronic nephritis. Heuer freed the renal vessels and after visualizing the sympathetic nerves, removed the nerves from both the ventral and the dorsal aspects of the vessels. In the one patient suffering from severe essential hypertension, the operation failed to alter the level of the pressure or to improve the function of the kidney. In patients with nephritis the blood pressure was lowered for a few weeks after operation, but in all except 1 case it then regained its original level. The urea function of the kidney remained essentially unchanged; two of the patients exhibited increased concentrating power.

**Section of the Splanchnic Nerves.**—This procedure has already been discussed in connection with denervation of the adrenals (p. 1356).

**Spinal Nerve Root Resections.**—This operation, proposed by Adson and Brown,<sup>42</sup> consists in sectioning the anterior and probably also the posterior nerve roots from the sixth thoracic to the second lumbar segment. Even with such an extensive influence on vasomotor control and on intra-abdominal pressure, the result was not striking. Page and Heuer<sup>43</sup> report that following this type of operation in a young girl the arterial pressure returned to normal for seven months. Dr. Brown<sup>32</sup> at present believes that in the malignant forms of hypertension the procedure has no influence on the course of the disease, but that in benign hypertension good results have been observed as late as five years after operation.

It is important to remember that in male subjects bilateral complete lumbar sympathectomy will induce sterilization. The patient will be able to perform the sexual act, with orgasm, but without ejaculation.

**Combined Surgical Measures.**—Finally, attempts are being made to investigate the effect of various combinations of the methods described above. The possible value of such a procedure can be surmised from the foregoing discussion.

#### CRITIQUE OF THE SURGICAL TREATMENT OF ARTERIAL HYPERTENSION

The following points have been, or may be, proposed in favor of the surgical treatment of primary (essential) hypertension: (1) there is an increased secretion of adrenalin which is responsible for hypertension. (2) Primary hypertension develops secondarily from a primary pathology in the kidney and is precipitated through afferent nervous impulses from the kidney. (3) There is a hyperactive vasomotor center in hypertensive patients with resulting increased motor nerve impulses and exaggerated pressor responses. (4) Even if there exists no increased vasomotor tonus in hypertension, an induced reduction of the normal tonus is desirable in view of the fact that the vascular system is hypersensitive to normal nervous and chemical stimuli. (5) Elevation of the arterial pressure produces wear and tear on the arterial and arteriolar systems; hence reduction of the arterial pressure *per se* is a beneficial procedure.

The following points bearing on these proposals must, however, be considered: (1) as far as cases of essential and of nephritic hypertension are concerned, there is no evidence that increased secretion of adrenalin is present. (2) Similarly, there is no evidence that essential hypertension is of renal origin, and surgical denervation actually fails to influence the state of essential hypertension. (3) There is inadequate evidence up to the present time to suggest that the efferent vasomotor impulses exert a greater constrictor effect in hypertensive than in normal subjects. Recent experimental evidence indicates that the vasomotor tone is not increased above normal in hypertension.<sup>7</sup> (4) If the normal vasomotor tonus could be diminished diffusely in all organs without influencing deleteriously the essential physiologic responses, this would be beneficial. Thus far, however, this has not been accomplished. The decrease of vasomotor impulses within one region of the body, on the other hand, may well have a deleterious effect on the function of other organs in which the constricted state

of the arterioles persists, and in which now, as a result of the decreased blood pressure, a *suboptimal* blood flow will exist. (5) The studies of Cannon and his associates<sup>44, 45, 46</sup> have demonstrated that the blood pressure responses of animals following various types of sections of the spinal sympathetic and splanchnic nerves are not uniform, and that they vary in different species of animals. Even after complete exclusion of sympathetic control of the blood vessels the blood pressure, after a postoperative drop, returns to approximately normal level. (6) While it is true that elevated arterial pressure represents wear and tear, it is equally true that persistent elevation of the capillary pressure may represent even greater wear and tear on these delicate vessels. It should therefore be appreciated that if one induces splanchnic arteriolar dilatation through nerve section, marked capillary hypertension will be precipitated. Thus we have shown that the local dilatation of an arteriole with histamine will elevate the normal capillary pressure in hypertension of 12 to 108 mm. Hg.<sup>6</sup> It is questionable whether the benefit of the moderate drop in the systemic arterial pressure, claimed to result from the denervation, can outweigh the possible damage to the visceral organs, which will have to function under active hyperemia and under increased capillary pressure.

Granted that all the foregoing objections, based on experimental and clinical studies, can be obviated, there still remain the following fundamental facts enumerated earlier in this discussion, namely: (1) *arterial hypertension is primarily a progressive obstructive disease of the arteriolar system over the entire body*; (2) *the blood flow in the tissues in hypertension is practically always optimal or already suboptimal*; (3) *the elevation of the arterial pressure is a homeostatic adaptation on the part of the body for the purpose of maintaining optimal blood flow to the tissues at rest and under physiologic stress*. Suppose one effectively lowers the arterial pressure through splanchnic vasodilatation, one certainly cannot claim to influence the progress of the arteriolar constriction in the brain, heart, muscles and other organs. May not these patients ultimately predispose to cerebral and coronary thrombosis? From what we know regarding the compensatory capacity of the peripheral circulation in heart disease,<sup>47</sup> there



may be increased utilization of oxygen for a while and the symptoms may be masked, but the limit of peripheral circulatory adaptation will be reached. Thus, complications, which may be expected, will not become evident within from six to twelve months, the average period of observation in the majority of papers published.

The alleged symptomatic improvement of some patients does not necessarily justify such severe and far-reaching surgical interference as is advocated by many. One may lower the blood pressure and may abolish symptoms, but at the same time may also shorten the life of the patient, who otherwise might have lived for years in fair health. I do not wish to imply that it can be stated definitely that the surgical procedures advocated in recent years are dangerous or indifferent in their results. The conclusion seems justified, however, that adequate evidence as to whether the benefit of surgical measures outweighs their possible harmful effect has not been presented as yet. It is also obvious that some of these measures have been proposed either on false or on unproved premises or without proper appreciation of the clinical nature of hypertension, a condition which shows marked and irregular fluctuations in its course, and in which spontaneous and even permanent lowering of the arterial pressure is not a rare occurrence.

Surgery of the sympathetic nervous system has introduced some significant therapeutic measures, but it has also demonstrated numerous failures, so far as practical measures are concerned. For the practitioner, who primarily cares for the patient, this is important to appreciate. Investigation has to progress through intelligent and justified trial and error. It is wise, however, that physicians should accept therapeutic claims and particularly new surgical procedures only after proper evaluation of the problem and when there is strong supporting evidence. In case of arterial hypertension the presentation of such therapeutic proof is at best difficult. For the present, therefore, it seems advisable to leave the surgical treatment of arterial hypertension in the hands of those surgeons who believe that they can answer the problems raised in this discussion and who can eventually present adequate proof that there is lasting benefit to their patients.

## V. CONCLUSIONS

Whereas some of the drugs described are effective in the relief of symptoms in hypertension and of vascular crises or other vasospastic states, an analysis of the evidence presented justifies the conclusion that the majority of them do not fulfill the therapeutic requisites outlined, and that their routine use in hypertension is therefore not advisable.

The value of the surgical procedures practiced recently for the relief of hypertension cannot be considered as established. Several important aspects of this problem have yet to be clarified.

Hence the rational management of hypertension consists in intelligent environmental management of the patient by means of rest periods, diet, psychotherapeutic guidance and sedation. The numerous complications of hypertension should receive specific consideration.

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### THE TREATMENT OF GONOCOCCAL ARTHRITIS, RHEUMATOID ARTHRITIS, AND GOUT

THE current medical literature contains numerous papers concerning the treatment of arthritis. Indeed, it is often difficult to evaluate many of the remedies suggested, since the type of joint disorder is not defined and the natural history of the disease is not taken into account when summarizing the results. It is no exaggeration to say that the adequate treatment of any disease can be carried out only if its cause is known. In many cases of chronic arthritis, and especially the rheumatoid type, the cause remains in doubt so that it becomes necessary to manage the patient in the most practical way. The treatment of any chronic illness is of necessity schematic in type and it must be based upon a rational and conventional diagnosis. In dealing with chronic arthritis, the treatment has the following objectives: (1) the relief of discomforts; (2) safeguarding the patient from deformities and increasing the function of the injured joints; (3) prevention, if possible, of the progress of the disease.

At the outset, it should be remembered that many of the procedures advised by the physician will require readjustment of the individual to the limitation of his or her activity which they must be taught to recognize. This requires considerable thought, tact and sympathy upon the part of the physician, and the best results are frequently obtained by paying meticulous attention to details.

In the evaluation of treatment, one must not forget the natural history of the disease. The question is frequently

asked by physicians—what would be the natural course of events if no particular form of treatment were given? The answer to this question has never been given, since practically all patients with arthritis receive some form of treatment. It is known, however, from the study of large groups of cases, that a certain number of patients, usually around 80 per cent, improve temporarily at least, regardless of the type of therapy employed. In these individuals the disease is relapsing in nature and may continue for years. In others, the disease advances without remissions and in spite of all available treatment. It is well, then, to take these facts into consideration before attaching too much significance to one type of treatment as a method of choice to the exclusion of others.

At this time the treatment of gonococcal and rheumatoid arthritis and gout will be discussed in the light of present-day concepts of these maladies.

#### GONOCOCCAL ARTHRITIS

As far as we know, gonococcal arthritis is a true metastatic synovitis, but the tendon sheaths and other tissue of the body may be involved at the same time. The course of the disease, once it is established, may vary tremendously, depending upon the severity of the infection, the joints involved, whether or not reinfection occurs before recovery takes place, and the mode of treatment employed. In any event, the illness may last several months, causing great economic loss and in not a few cases, permanent damage to the joints. In the cases in which permanent damage takes place, there is usually damage to the articular cartilages during the acute phase of the disease, whereas if the disease is confined to the synovia the end-results may be better insofar as function is concerned. The treatment is carried out along the following lines:

1. Treatment of the primary focus.
2. Absolute rest of the joints during the acute phase.
3. Aspiration or irrigation of joints.
4. The use of fever therapy.
5. General upbuilding treatment.
6. Prevention of deformities.

When the knee or other large joints are involved in

gonococcal arthritis, and aspiration of the synovial fluid reveals a leukocyte count above 40,000 per cubic millimeter, and there are micro-organisms present, we usually advise the irrigation of the joint through a small incision in the capsule. It is especially important if the fluid is difficult to aspirate and contains large amounts of fibrin. After the joint has been washed out it is closed tightly, the knee is placed in traction and motion is started as soon as it is possible to do so without pain or discomfort. Our results with this method of treatment have been very satisfactory, with the immediate as well as the ultimate results.

The use of fever therapy either by the injection of typhoid vaccine or other methods has received an enthusiastic reception by many observers. It seems clear from the reported cases<sup>1, 2, 3</sup> that hyperpyrexia seems to be most effective in the treatment of this type of arthritis. Five to seven treatments have been recommended and the temperature is elevated to 106° or 107° F. for five or six hours, every three to five days. The results of various authors have been summarized by Hench, Slocumb and Popp,<sup>1</sup> Schnabel and Fetter.<sup>2</sup> It appears that the best results are obtained in patients with acute gonococcal arthritis of short duration, and less striking results are obtained in the subacute or chronic types of cases. From the reports in the literature it would seem justifiable to use fever therapy in this type of arthritis more often in an attempt to learn more about the ultimate results of the cases treated in this way.

As one observes patients with gonococcal arthritis, it becomes apparent that many of them lose large amounts of weight and develop anemia, the muscles atrophy about the affected joints and the patients present the clinical picture which is so common in chronic infections. In our experience, blood transfusions for anemia and a liberal intake of food is highly desirable in such cases. The general upbuilding treatment is often of the highest importance.

When the above measures are followed, the results of treatment of gonococcal arthritis are usually satisfactory as far as the end-results are concerned. The course of the illness is often slow and even with the best of care, poor results are occasionally seen.



The convalescence is often difficult to manage and prolonged; efforts should be directed along the following lines:

1. Rebuilding muscle tone and strength about the affected joints.
2. The support of the arches of the feet, especially if the knees have been involved and the patient has been confined to bed for a long period of time.
3. Instructions regarding venereal disease prophylaxis.

### RHEUMATOID ARTHRITIS

The cause of this type of arthritis is unknown. For this reason there is no adequate form of treatment for the condition. It is a malady characterized by remissions and relapses and there is no satisfactory evidence that any of the many remedies suggested are in themselves responsible for altering the course of the process. To be sure, many types of treatment are recommended, so that scarcely a year passes without the introduction of several new remedies. In the present state of our knowledge all one can hope to accomplish is to relieve the patient of as much discomfort as possible, to prevent the development of deformities when possible, and to give the patient the best possible opportunity of recovering from his disease through general upbuilding treatment and the correction of any abnormal functional disorders that may be present. It is highly important to discover, when possible, any factor that makes the patient worse. This can be done by questioning the patient and observing the course carefully. When these factors are discovered they should be eliminated.

**Symptomatic Treatment.**—The best form of symptomatic treatment is rest, especially rest in bed or absolute rest of the affected joints. Many patients maintain that the one thing that makes them worse is fatigue. The relief of pain can be accomplished by the use of drugs, the proper application of splints and supports to relieve muscle spasm, and the judicious use of local heat to the affected joints. Of the drugs which give most relief, the various salicylate compounds, and the atophan group are most effective. The latter group of drugs should be used with caution, since one occasionally encounters sensitivity to them.

Splints and support of affected joints should be applied early in order to relieve muscle spasm and prevent deformity. If deformity is inevitable, then the joint should be fixed in the most desirable position. These are problems that must be worked out in cooperation with the orthopedic surgeon.

**General Upbuilding Treatment.**—*Regulation of Activity.*—It is a good plan to keep the patient's joints at rest as long as there are any signs of inflammation present in the synovial membrane. The constant use of a joint which is the site of an inflammatory process only tends to increase the irritation and propagate the process. When the acute process subsides, exercise may be allowed within the limitations of the individual's ability to do work without fatigue or pain.

*Diet.*—One of the commonest questions that patients who have arthritis ask the physician is—what can I eat? Some physicians are of the opinion that altering the diet in various ways is of the highest importance in bringing about improvement; but aside from the cases in which there is a definite idiosyncrasy to certain foods there is little convincing evidence that high carbohydrate or other types of diet are responsible for the patient's symptoms. This question has been discussed at some length and in a critical fashion by Bauer, who concludes that "patients with rheumatoid arthritis should take a diet high in calories (unless they are overweight), high in vitamins and adequate in respect to calcium, phosphorus and iron." He points out that there is no convincing evidence that proves that a low carbohydrate diet is indicated in this disease, and that there is no proof that it is efficacious in curing the disease. With these conclusions I am in complete accord.

*Removal of Foci of Infection.*—The safest rule to follow in regard to foci of infection is to have them removed for their own sake rather than for the arthritis. By doing this, the patient is sometimes assisted in making a more rapid recovery. Before advising such procedures, definite evidence for the existence of infection should be present and the patient should be informed that such operations may be helpful but they may not necessarily be followed by improvement of the arthritis.

**Miscellaneous Treatment.**—*Anemia.*—When anemia of the hypochromic type is present it should be treated with iron, and in the cases in which it seems desirable to increase the hemoglobin or red blood cells more rapidly, whole blood transfusions may be given. The latter method has been used especially by Dawson and Boots.

*Fever Therapy.*—From time to time, various forms of fever therapy are used in the treatment of arthritis, including the artificial induction of fever with malaria, typhoid vaccine, diathermy, hot boxes, air-conditioned cabinets and so forth. Within the past year several excellent reviews of this subject have been presented by Hench, Slocumb and Popp, and Short and Bauer. As far as rheumatoid arthritis is concerned, there seems to be general agreement that the results obtained are of a temporary nature. Short and Bauer report that 80 per cent of their patients showed temporary improvement, but that this was maintained in only 20 per cent of individuals at the end of a two-year period or longer. The patients who seemed to respond most favorably were young individuals with arthritis of short duration, with little or no cartilage destruction, and with marked vasomotor changes who showed an increase in pulse pressure during treatment. They were of the opinion that the improvement in these patients was due to increasing the blood supply to the affected tissues. They concluded that this method of treatment was only occasionally justified and should not be used to the exclusion of general treatment.

From a review of the literature on the subject of fever therapy in rheumatoid arthritis, together with the results of personal observations, Hench, Slocumb and Popp came to the conclusion that the value of fever therapy could not be fully appraised at the present time. They expressed the opinion that a trial of fever therapy is justified in "selected" cases. Of 60 patients treated in this way, 70 per cent got little or no relief and the remaining 30 per cent received significant benefit.

A recent paper by Cecil, Freiss, Nicholls and Thomas<sup>4</sup> relates their experience with malarial treatment of 13 cases of rheumatoid arthritis. All of their patients received temporary symptomatic improvement with disappearance of pain

and swelling after three or four malarial paroxysms. Within a period of six months after the termination of this treatment, 12 of the 13 patients had a return of their symptoms, but in four of these the general condition was thought to be better than before the treatment. The only patient who had not relapsed during the period of observation had had arthritis only four months before the treatment.

In brief, then, it appears that a small number of patients with rheumatoid arthritis are temporarily relieved following fever therapy. The experience so far would indicate that the improvement is lasting in only a few and that it is most striking in young individuals with arthritis of short duration, with marked vasomotor disturbances, but without cartilage destruction. It should be added that it is a procedure that must be carried out by a physician and a skilled nurse, since it is not an altogether harmless procedure. Hyperpyrexia and death have been reported.<sup>2</sup>

*Vaccine Treatment.*—This method of treating rheumatoid arthritis has been used widely for a number of years. In some instances vaccines have been employed to increase body temperature; in other cases, they have been injected in an attempt to increase the patient's immunity to certain strains of streptococci or to decrease his sensitivity to the products of these organisms. The strains of organisms used have been derived from the patient and attempts have been made to select the various strains on a basis of the patient's reaction to skin tests made with these organisms or by determining the presence of complement fixation bodies in the circulating blood. All of these procedures are based upon the assumption that rheumatoid arthritis is due to a streptococcal infection, and while there is some evidence to support such a conclusion, it is far from being settled. This question has been discussed in detail elsewhere and need not be repeated here.

The results of vaccine therapy are controversial. The recent observations of Wainwright<sup>5</sup> indicate that 21 of 28 cases of rheumatoid arthritis showed improvement following intravenous injections of streptococcus vaccine prepared from the strain to which the patient was most sensitive. As objective evidence for the improvement, there was a relief of

pain, a reduction of soft tissue swelling and increased mobility of the joints, together with a uniform decrease in the skin sensitivity and an increase in the agglutinins in the blood of some patients.

Boots<sup>6</sup> has recorded the results of his experience by saying that the value of vaccine therapy remains unproved. They have not been able to influence favorably the sedimentation rate of the erythrocytes, and other forms of treatment are followed by as great a clinical improvement as those on vaccine therapy. He expressed the opinion, however, that one can do no harm in trying it.

From the reports of vaccine therapy and from personal experience, it would seem that vaccine treatment should be tried in individuals in whom the arthritis has been preceded by an infection, and in whom one is able to demonstrate agglutinins and skin reactions to hemolytic streptococci. It will be generally admitted that it should not be used to the exclusion of general upbuilding treatment.

*Sulphur Treatment.*—Within recent years collodial sulphur has been used extensively in the treatment of arthritis. A recent paper by Rawls, Gruskin and Ressa<sup>7</sup> records their results with this drug in a miscellaneous group of patients with arthritis, and summarizes the studies of others. They concluded that sulphur was a valuable agent in the treatment of arthritis, in spite of the fact that they did not feel that it was of much benefit in young people with rheumatoid arthritis. When improvement was noted, it occurred in older individuals with rheumatoid arthritis and in patients with "mixed arthritis and osteoarthritis." In these patients the cystine content of the fingernails was said to be low and "sulphur treatment is often beneficial."

One gains the impression from this paper as well as from others that the use of sulphur in the treatment of arthritis is purely empirical and that the evidence brought forth to support its use as a valuable agent in the treatment of arthritis is not very convincing, as far as the ultimate results are concerned.

**Management of Convalescence from Acute Arthritis.**  
—This phase of the treatment of arthritis demands great attention since the individual's progress can be accelerated by

intelligent management. Fundamentally it consists in building up muscle tone and the structures supporting the affected joints by exercises and physiotherapeutic measures, and the use of various types of apparatus that may aid in the support of joints. The principles and methods that are used for the different joints have been outlined by Ober,<sup>8</sup> and since the importance of these procedures are in following certain details, his paper should be consulted.

### GOUT

The treatment of gout can be divided into three groups: (1) the acute attack; (2) the interval treatment; (3) chronic gout.

By general consent, it is agreed that the pain of acute gout is most severe, and may require large doses of such sedatives as opium to control it. The following procedures should be carried out: (1) Rest in bed. (2) Protection of the affected joints. (3) Forcing fluids to 3000 cc. a day. (4) Administration of purges in the form of wine of colchicum and tincture of rhubarb until a free diarrhea is obtained. (5) The use of atophan, alkalies and salicylates. (6) A diet that is high in protein and carbohydrate but low in fat and purine.<sup>9</sup>

Once the acute attack has subsided, it is well to advise the patient regarding factors that aid in preventing attacks. In many cases, the patients with gout know only too well what brings on their attacks; in others, they, as well as the physician, are unaware of the cause of an acute attack. Such conditions as dietary indiscretion, excessive fatigue or trauma to the various joints should be avoided. In addition, adequate care should be taken to see that these patients remain on a low purine, low fat diet with liberal amounts of protein in the form of milk, eggs, cheese, and an adequate amount of carbohydrate. Alkalies, salicylates and cinchophen are also recommended in small doses and the fluid intake should be such as to give a dilute urine. Since these patients often have attacks following surgical operations, they should be prepared before operation by the treatment outlined above and by a low purine diet.

**Chronic Gout.**—The measures outlined above are used in the treatment of chronic gout, but in some cases in which

there are large deposits of urates in and about the joints, the treatment is unsatisfactory. I have recently observed a patient who has had attacks of gout for forty-six years, and at present he is completely incapacitated on account of the great deformity of his hands due to the deposits of urates, the destruction and ankylosis of some of the terminal phalanges. He informs me that only two things give him relief; one is colchicum and the other is the relief of tension in the affected joint that follows a puncture wound and the expression of urates. In these cases, treatment continues to be unsatisfactory and the nature of the disease needs further investigation.

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## CLINIC OF DR. J. H. MEANS

FROM THE THYROID CLINIC OF THE MASSACHUSETTS  
GENERAL HOSPITAL

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### TREATMENT OF DISEASES OF THE THYROID

I HAVE been asked to give a clinic illustrating by means of cases some of the problems involved in the treatment of diseases of the thyroid—recent advances in the treatment of these diseases, in fact. I am not aware of any very recent advances in this field, at least, none that have got beyond what might be called an experimental stage. It is greatly to be hoped that we soon shall have a nonsurgical method of curing thyrotoxicosis and from the interrelationships of pituitary thyrotropic hormone and antihormones, in the sense of Collip, should the existence of these finally become well established, we have reason to hope that a nonsurgical treatment will presently emerge. Reports of remedies of this kind are to be found in the German literature, but their value has certainly not yet been established beyond all question. From a practical point of view we still find ourselves in the situation we have been in for some years, which is that subtotal thyroidectomy, during a period of full iodination is the best therapy we can advise for our patients suffering from toxic goiter.

Nor has anything very new recently emerged in the treatment of myxedema. In dried thyroid gland we have for years possessed an ideal treatment for the hypothyroid states and experience over a number of years has indicated to us that the wisest policy to follow is that of placing the patient on the minimum ration of dried thyroid, by mouth, which will rid him completely of all symptoms and signs of myxedema.

In the field of thyroid diseases not accompanied by change



in the function of the gland, which includes simple goiter, nontoxic nodular goiter, malignant goiter and inflammatory goiter, the principles of treatment consist in surgical removal when any of the following indications are present: (1) pressure; (2) suspicion of malignancy; or (3) unsightliness which troubles the patient; and occasionally irradiation in some form or other, either alone or in conjunction with surgery, in certain of the malignant cases.

It obviously is impossible, in the space allowed, to illustrate by cases all these different problems. Because the routine care of the various types of thyroid disease has been thoroughly discussed in previous clinics in this series as well as elsewhere,<sup>1, 2, 3, 4, 5, 6</sup> I have decided that the best use to which to put the present clinic is that of illustrating how one works out the indications for treatment in some of the puzzling, complicated or atypical cases.

Let us begin with the case of Miss B. This patient, a lady of forty-three, consulted me first on March 25, 1935. She had had a subtotal thyroidectomy for exophthalmic goiter in a Middle Western city in February of 1933. In the autumn of 1931 she had had grippe and following this was in a rundown condition. Metabolic tests had been made showing a result of -7 and thyroid had been ordered. She had taken this for six weeks. According to her story it had had no noteworthy effect. In the summer of 1932 she had taken a trip abroad and had become very fatigued as a result. For this she again took thyroid intermittently. In the autumn of 1932 it was found that she was losing weight rapidly and having rapid heart action. She was seen in a private clinic in Boston and states that she was there told that she had no thyroid trouble. She continued to feel badly, however, and while visiting in the Middle Western city the diagnosis of exophthalmic goiter was made and operation performed as I have already stated.

Following her operation she was better in general but it took a very long time for her to get her strength back. She had been placed on Lugol's solution prior to the operation and had continued to take it ever since. During the year before I saw her, her eyes had become increasingly prominent. Her major symptom was fatigue. During the autumn of 1934 she had been so exhausted that she was almost bedridden for three months. She not infrequently had palpitation, but didn't sweat much. She had lost 3 or 4 pounds since the previous Christmas. Two weeks before she came to me she had a bout of diarrhea. She had had such bouts before operation but none since. Her catamenia were regular but scanty and brief. There was nothing in her past or family history that seemed to be significant.

My physical examination on March 25, 1935 showed a startled looking, middle-aged, thin woman who did not act in the slightest degree as though she had thyrotoxicosis. She had bilateral exophthalmos, more on the left than on the right, of moderate degree, bilateral lid lag, but no irritation of her corneae. She had no tremor and her hands were cold and dry. No thyroid

tissue could be palpated, no bruit could be heard in the neck, but a thrill could be felt in the region of the right lower pole of the thyroid. Her heart was rapid—rate 100, but not enlarged, rhythm was normal and there were no murmurs. Her blood pressure was 110/90. The remainder of the physical examination showed nothing of significance. She gave the impression of being a very lackadaisical, languid person. I may add that she was a lady of means and leisure, apparently without responsibility, whose chief interests in life were gardening, music and church work.

It was my very definite impression, when I first saw her, that she was not thyrotoxic, that she had no return of her Graves' disease and that her symptoms were upon a psychoneurotic basis—something which might be called, perhaps for want of a better name, effort syndrome. I was convinced that she had had exophthalmic goiter in the past because of the presence of the definite eye signs.

I obtained a metabolic rate determination which on April 2, 1935, showed levels of  $-5$  and  $-10$  for two consecutive periods. This seemed to square with the impression that she was not thyrotoxic. I ordered her to stop her iodine and then sat tight to see what would happen. What did happen was of great interest. On April 12 her metabolic rate had risen to  $+17$  and on April 13 it was  $+25$ . Coincidentally with this her symptoms became greatly intensified. She became weak to the point of exhaustion and her pulse rose to a level of about 115; her skin became warm and sweaty. At this time a small amount of thyroid tissue was felt in the region of the isthmus.

The picture, therefore, had undergone an important change since the omission of iodine. There seemed little doubt at this time that she was thyrotoxic and that this thyrotoxicosis had supervened upon the omission of iodine. The natural further deduction was that she had been potentially thyrotoxic all along, probably ever since her operation, but that this thyrotoxicosis was a residual of rather small proportion which the ration of iodine was able to hold partially in abeyance. Dr. Arthur W. Allen was called in consultation and he agreed that the case was probably one of persistent and recurrent thyrotoxicosis and that further resection of thyroid tissue was indicated. A second operation was done on April 23, 1935. This operation was subtotal thyroidectomy upon the remaining tissue. A piece of thyroid about 5 cm. long, 2 cm. wide and  $1\frac{1}{2}$  cm. thick was dissected out from the neighborhood of the right side of the trachea and the region of the isthmus.

The histologic picture of this removed tissue was that of definite parenchymatous hyperplasia with considerable colloid storage in places. This anatomic finding, therefore, confirmed the clinical impression of recurrent exophthalmic goiter.

The patient went through the operation very smoothly and on May 1, 1935 the metabolic rate was  $-11$ , on May 6 it was  $-20$ . At this time the patient was still taking iodine—Lugol's solution, 5 minims once daily. On that day she was discharged from the hospital and iodine was omitted.

I have seen her from time to time since and on the whole she has been considerably improved, although there are periods when her old feeling of weakness seems to return. On September 24, 1935, metabolic rate was  $-15$ . I saw her on that date and my impression was that she was essentially well.

This case impresses me as being distinctly instructive. In the first place it was proved that persistent or recurrent thyrotoxicosis was present in spite of the fact that the patient

was running a metabolic rate below standard and presented symptoms which were by no means characteristic of thyrotoxicosis. Treatment necessarily hangs upon diagnosis. In this case the diagnosis was established by means of an iodine test carried out in a manner the reverse of that usually practiced; instead of noting the result of giving iodine, in this case, we noted the effect of omitting it. As soon as it was omitted the low grade thyrotoxicosis which the iodine had masked, manifested itself quite clearly.

On the first consideration of the case it would have seemed ridiculous to propose a second thyroidectomy for toxic goiter when there were no thoroughly characteristic symptoms, a slightly minus metabolic rate and very little thyroid tissue to be felt. None-the-less, it turned out that that was the correct treatment and the final result has proved this.

One may draw the general conclusion that before planning treatment in any thyroid case, the true level of functional activity must be determined and oftentimes this can only be done by giving or omitting iodine, or indeed doing first one and then the other.

Let us next consider the case of Mrs. B., a woman sixty-nine years old, who entered the hospital under my care on June 15, 1934, referred by Dr. Paul D. White. Dr. White had had this patient under observation since October, 1927, at which time he had made a diagnosis of irritable, slightly hypertensive heart with many ventricular premature beats. He had also observed at that time a slight enlargement of the thyroid with slight bruit. He had seen her at intervals since and she had always shown ventricular premature beats and some nervous symptoms. Nothing had happened, however, until a few weeks before entry when seeing her at her home Dr. White found she was losing weight rapidly and having tachycardia with many premature beats and a very full pulse pressure. He considered that thyrotoxicosis was very likely present.

Upon Mrs. B.'s entry to the hospital I did my best to decide at Dr. White's request (1) whether she was thyrotoxic, and (2) whether, if she were thyrotoxic, she was fit for operation. My physical examination at the time of entry disclosed a woman, not obviously hyperactive with none of the eye signs of exophthalmic goiter, with very slight tremor and with a thyroid isthmus and lateral lobes just barely palpable. Her heart was enlarged and fibrillating. No gross edema could be found anywhere. She was not orthopneic. The remainder of the physical examination was not highly informative.

She was put to bed and observed. The following metabolic rates were obtained: June 16, 1934, +33; June 19, +39; June 21, +35; June 23, +38; and June 26, +34. The maintenance of this elevated level in the absence of gross congestive heart failure was strong presumptive evidence of thyrotoxicosis. It was determined to observe the effect of giving iodine. After five days of

iodine, no fall whatever was noted in the metabolic rate level. The iodine was begun on June 22. Digitalis had been begun the day before. Under the influence of these two drugs the pulse rate slowly fell from a rate of about 120 to one under 100. There was no means of determining which drug was chiefly responsible.

I had been very dubious of the evidence of thyrotoxicosis at entry and recorded that opinion in the hospital record, however, after observing the level of metabolic rate I began to question the accuracy of this conclusion. The failure of her metabolism to drop in five days on iodine was inconclusive one way or the other. Further metabolic rate determinations should have been made, but since the tests distressed the patient considerably they were omitted.

Because of Dr. White's feeling that the heart condition was best explained by thyrotoxicosis, and because the surgeon, who saw the patient in consultation, believed that he could do a thyroidectomy successfully (he stated the risk was about five times the normal, however), and because the family were eager to leave no means of treatment unused that offered any hope of relief, I finally consented to operation on her thyroid. This was done on July 2, 1935. The operation itself went extremely smoothly. The patient returned to her room in excellent condition. The operation actually was a subtotal thyroidectomy. There was found at operation a very small right lobe, also an enlarged isthmus, a moderately sized pyramidal lobe on the left and a large left lobe. The patient did not long continue to do well after operation. She became gradually weaker, her pulse and temperature steadily climbed and she died the third day after operation. Unfortunately no autopsy could be obtained.

Finally a very important finding was that the pathologic examination of the thyroid showed no evidence of hyperplasia, merely the picture of colloid goiter, or so-called involution. As we look back over this case we can not escape the feeling that the operation was very likely not indicated. We learn by our errors. One error here was certainly in terminating the period of observation before the response to iodine or lack thereof had been definitely established. But even had this been done we might still have found ourselves in difficulties. How would we have interpreted a persistently high metabolic rate in spite of full iodination? One interpretation would have been that thyrotoxicosis was not present. One cannot, however, say categorically that failure to respond to iodine absolutely excludes overactivity of the thyroid. There are cases, undoubtedly thyrotoxic, who fail to show an iodine response, perhaps because the iodine is given at a time when their thyrotoxicosis is undergoing natural intensification. Mrs. B.'s story would have been consistent with such an interpretation. Had a good response to iodine been obtained, we should have felt that the indication for operation was much clearer. It is a pity that we didn't carry on long enough to give an opportunity for an unequivocal answer to our test. It is doubtful whether, had we left her unoperated, she would have lived very much longer. The cardiologists' opinion was that her outlook without operation was distinctly poor. That was one reason why it seemed rational to take a fairly desperate chance. In retrospect I regret that an operation was undertaken. I should rather have had her die unoperated than apparently as a result of surgery. The question also comes up as to whether multiple operation might have been better for her. I think this is possible, but not likely. It is my belief that the same outcome would have obtained had only a small portion of the goiter been removed as a preliminary procedure. This, however, is a point which cannot be settled.

Let us pass now to the case of Mrs. M., which I should like to contrast particularly with the case of Mrs. B. Mrs. M., a widow of fifty-nine, entered the hospital on November 29, 1934. She came in complaining of nervousness and fatigue for several months, emotional instability and recent weight loss. On physical examination she showed a warm, moist skin, definite tremor of her fingers, an enlargement of the isthmus and left lobe of the thyroid, but no eye signs characteristic of exophthalmic goiter. It was not possible to say, on the evidence which she presented, that thyrotoxicosis was present but there was a very definite suspicion of it. On November 30 her basal metabolic rate was found to be +49 and it was determined to conduct a diagnostic test with iodine. After iodine had been started the following metabolic rates were obtained: December 1, +47; December 3, +37; December 4, +42; and December 5, +40. On the latter day iodine was omitted. On December 10 the metabolic rate was +28; on December 12, +48; on December 13, +34; on December 14, +39; on December 15, +38; on December 17, +32 and on December 18, +32. On December 21 iodine was started again—potassium iodide, 10 minims once a day. On December 22 the metabolic rate was +46, on the 26th it was +40, on the 29th it was +43, on the 31st it was +31, on January 2, 1935, it was +30 and on January 4 it was +31. In other words, there was absolutely no indication that her condition was better while taking iodine than while not taking it. The iodine test was frankly negative. Nevertheless, it was felt that the clinical picture better fitted thyrotoxicosis than anything else and as the patient was not improving it was finally decided to resort to surgery. On January 5, 1935 a subtotal thyroidectomy was performed, which the patient stood very well. A considerable portion of both lateral lobes and isthmus was removed. The histologic examination of the tissue removed showed the type of hyperplasia characteristic of exophthalmic goiter with considerable colloid storage, that is to say involution. The patient made an uneventful recovery and on the 16th of January her metabolic rate was +2.

Mrs. B.'s case and Mrs. M.'s case furnish some interesting similarities and contrasts. The metabolic rates of the two were running at about the same level and in neither case did we establish any improvement as a result of giving iodine. We held off on Mrs. M.'s operation for a considerable period of time, largely because of the experience with Mrs. B. I felt that the failure to respond to iodine might, on the one hand, indicate that she wasn't thyrotoxic or, on the other, that if thyrotoxic she would be a poor operative risk. Both of these interpretations were incorrect. It turned out that she was definitely thyrotoxic and she did go through operation very smoothly. The presence of the serious heart disease in Mrs. B., of course, made the problem a much more difficult one than in Mrs. M., whose heart was apparently normal. Taken together, the cases may be said to teach us that while the iodine test is very helpful, it is not to be looked

upon as finally giving the absolute indication to treatment in all cases. In this respect it is not different from any other diagnostic test which we employ for a similar purpose.

We may now pass to another case, this one of proven thyrotoxicosis which presented some interesting difficulties. Mr. S., a widower of forty-six, entered the Massachusetts General Hospital first on November 26, 1934, transferred from the Boston Psychopathic Hospital, to which institution he had been sent two months previous for some definitely psychopathic manifestations. In addition to these, however, he had an array of signs and symptoms classic of exophthalmic goiter, and it was for that reason that he was sent to us. Examination and history further disclosed that he was suffering from rheumatic heart disease with involvement of both mitral and aortic valves, congestive heart failure and auricular fibrillation. He had moderate exophthalmos and lid lag, a very wild expression, a small firm goiter with very loud bruit, warm skin which was moist except in the palms which were dry, and slight edema of the ankles. The diagnosis of exophthalmic goiter was evident, and also the complication of rheumatic heart disease with decompensation, and apparent psychotic manifestations.

When I first saw him I felt he should be iodinated at once and operated as soon as he was ready. I felt that to rid him of his thyrotoxicosis might rid him of all his troubles—thyroid, cerebral and cardiologic. His metabolic rate on November 27 was +43 and on November 30, +53. He made a good response to iodine, his metabolic rate dropping to about +30 and his symptoms showing marked improvement. He had a good diuresis, losing 10 pounds of weight, which was presumably water, and showed an amazing improvement in mental state. We felt that he was ready for operation when he developed a throat infection which necessitated its postponement. To make a long story short, this dragged on and on and to it was added a certain amount of bronchial infection which caused him to run a temperature of low grade for many weeks. During all this period iodination and digitalization were maintained. Also during all this period his mental state seemed to be quite normal. It was our belief that his psychosis was purely a manifestation of thyrotoxicosis. Finally, on the 18th of March, 1935, his infection having subsided considerably, an operation was performed. Because the surgeon was worried about his condition on the operating table, the removal was confined to the right lobe and isthmus, in other words, hemithyroidectomy. Histologically this tissue showed slight hyperplasia and marked involution. This doubtless was due to the prolonged iodination. He was discharged from the hospital on March 26, afebrile and in pretty good clinical shape, but with a metabolic rate still running at a high level—in fact, higher than before his hemithyroidectomy. Metabolic determinations had not been made for some time prior to the operation because of the presence of infection. After the operation they were running in the neighborhood of +60. The circumstances of his admission required that he be returned to the Boston Psychopathic Hospital for further observation, although during his long stay in the Massachusetts General Hospital he had shown no symptoms which impressed us as indicating any mental abnormality except those described just after admission.

On July 19 he was readmitted to the Massachusetts General Hospital to have a second operation upon his thyroid. At that time he seemed to be in very good condition, had gained 28 pounds and was showing no evidence of psychosis, but still had a metabolic rate in the +60s. On reiodination this

dropped to a level of  $+20$  and on August 6 his second hemithyroidectomy was performed. This he survived very well and on August 20 his metabolic rate was  $-2$ . On August 22 it was  $-13$ . Since then it has varied somewhat, often being within normal limits, but occasionally being up as high as  $+28$ . Following this second operation the patient became very much depressed and although this slowly improved, on October 18 he suddenly became violent and was discharged once more to the Boston Psychopathic Hospital.

This case brings up three factors which complicate the treatment of thyrotoxicosis: cardiac decompensation, mental decompensation, and respiratory infection. Indeed, we might add a fourth, namely, condition of the patient on the operating table which makes the surgeon unwilling to do more than a hemithyroidectomy.

I use the term "mental decompensation" advisedly. Just as the thyrotoxicosis adds a burden upon an already overloaded heart (overloaded by independent heart disease), so too may it add a burden to a brain potentially the seat of a psychosis and precipitate the same. As it has turned out this man seems to have a true chronic psychosis. Nevertheless, there is little doubt that the thyroid intoxication, working on such soil, created unusual havoc. Either the cardiac or mental complications in this case should be looked upon as indication for hastening operation to rid him of the extra burden which we have a way of removing.

The respiratory infection, upper and lower, which dragged on all winter, on the other hand, necessitated postponement of operation. However, by patiently waiting and maintaining iodination even this obstacle finally was overcome.

Finally, hemithyroidectomy is an unsatisfactory operation, because often it is necessary, as here, to follow it with a second resection. It is unpleasant, to say the least, for a patient to have his goiter out piecemeal.

This illustrates some of the vicissitudes of treatment. In spite of the several complications the outcome was good in all respects, except that there remained a residual psychosis, to which the psychiatrist gave the name of manic depressive.

The last case which I shall discuss presents a problem of quite a different nature. Mrs. S., a widow of sixty-six, entered the Massachusetts General Hospital first on June 22, 1922. Her story at that time was that for eight months she had gradually been losing strength and ambition and that occasionally she

had had attacks of dizziness. Furthermore, she had noted some swelling and puffiness in her face and her vision had appeared to her to be less acute. She had had increasing constipation and her skin had been getting dry and yellowish. These seemed to be the essential points in the history. Physical examination showed her to be obese and her face to present a strong suggestion of myxedema. The basal metabolic rate was determined on two occasions showing results of  $-34$  and  $-35$ . Her urinary and blood pictures were both within the range of normal. I was asked to see her in consultation, the particular question being, did I think she was suffering from hypothyroidism and if so, what therapy should she be given. My reply as it stands in the hospital record, dated June 28, 1922, is as follows: "Yes, in spite of certain atypical features, I think myxedema is very probably the trouble. I should get another metabolism test and then start her on  $7\frac{1}{2}$  grains of Burroughs Wellcome thyroid and in a week have another metabolism test. After that regulate dose in accordance with clinical picture and metabolism level."

It may be worth while to comment on the dose of thyroid which I then advised. Seven and a half grains is a perfectly proper dose of Burroughs Wellcome thyroid. Since this firm gives its dosage in terms of fresh gland it is different from the dosage which would be used of a brand of thyroid which conforms to the United States Pharmacopeia. It appears to be the total organic iodine content which determines the physiologic potency of thyroid preparations. Our study of various commercial brands of thyroid indicates that the following are approximately the same both as to iodine content and as to physiologic potency: Burroughs Wellcome, 5 grains; any U. S. P. brand such as Armour's, Lederle's, Hynson, Westcott and Dunning's or Lilly's,  $1\frac{1}{2}$  grains; or Parke, Davis, 1 grain. Therefore, the dose that I advised of Burroughs Wellcome thyroid would be equivalent to a  $2\frac{1}{2}$ -grain dosage of any U. S. P. preparation.<sup>7,8</sup> This is a little larger ration of thyroid than we advise at the present time. Our present custom is to use about 1 to  $1\frac{1}{2}$  grains of U. S. P. thyroid. In 1922 we rather felt that it was desirable to give enough thyroid to raise the metabolism to standard. At present we are content merely to rid the patient of symptoms, which can be done with such doses as I have just mentioned. Under these circumstances the metabolic rate is apt to be in the neighborhood of  $-10$  to  $-15$ .

Mrs S was placed on the dose of thyroid which I advised and her myxedematous manifestations cleared up. Thyroid was begun on June 30, 1922 and six days later her metabolic rate had reached  $-19$ . She was kept on this dose of thyroid until July 10, when it was raised to 12 grains of Burroughs Wellcome per day. She was discharged from the hospital on July 15, 1922, and on July 28 when she came into the clinic her metabolic rate was found to be  $-2$ .

She was seen from time to time in the clinic and remained well, thyroid therapy being continued. In February 1923 her metabolic rate was  $-3$  and in April of the same year it was  $-4$ . She then was lost sight of for a period of eleven years until December 2, 1934, when she was again admitted to the ward, sent in by a private physician. The story at this time was that she had continued taking thyroid somewhat irregularly. One year before this time she had begun to notice swelling of her ankles, which had gradually increased. Seven months before she had become weak in the legs and had massive edema which made it hard for her to get about. At this time, she stated, her physician told her she had heart and kidney trouble. He put her back on thyroid, but she says that it didn't give her much relief. At the same time she was put on diuretics. Two months prior to the last entry she began to have increas-



ing thirst and increasing micturition. Finally her physician told her that she had diabetes and sent her into the hospital.

Physical examination showed her to be very obese, with somewhat dry skin which had a faint yellowish tinge. Her heart was somewhat enlarged with a rough blowing systolic murmur heard loudest at the second right interspace. The liver edge was felt  $2\frac{1}{2}$  fingerbreadths below the costal margin and there was marked pitting edema of both legs. Her urine showed a moderate amount of sugar and her fasting blood sugar on several occasions was over 200 mg. My note on December 14 was as follows: "She apparently stopped thyroid about two months ago. She probably is coasting downhill metabolically. Now has  $-25$  basal metabolic rate which is a level of slight symptoms. If kept off thyroid, presently she will have symptoms. I should give her no thyroid till symptoms show up and then put her on a very small ration, say  $\frac{1}{2}$  grain (U. S. P.) once daily." I saw her again on January 4, and made the following note: "She still presents no clinical evidence of myxedema although off thyroid. Her diabetes is controllable thus far by diet alone. Her fasting blood sugar level is gradually falling. She may be continued off thyroid until clinical evidence of myxedema turns up." On January 8 Dr. J. H. Townsend, chief of our Diabetic Clinic, saw her and made the following note: "It seems as if she could be managed without insulin when she goes home. She is losing weight gradually on her present diet which should be continued pretty strictly." On January 11 she was discharged with a diagnosis of myxedema and diabetes mellitus. She was discharged with no medication and with a diet of C. 82, P. 58, F. 64. Her metabolic rate at this time was  $-23$ . We didn't see her again until August 26, 1935, when she was readmitted to the hospital. She had grown progressively weaker, had increasing constipation, puffiness of her face, dryness and scaliness of her skin, decreased tolerance to cold and diminution in the acuity of hearing. On physical examination she now had, in contrast to the previous entry, the appearance of full-blown myxedema. She was very bloated, with sallow yellowish complexion, round puffy face, coarse hair, sparse eyebrows, slow thick speech and big tongue. Her metabolic rate on August 29 was  $-30$  and on August 30  $-34$ . Her urine, however, showed no sugar and her blood sugar was 100 mg. I saw her on September 4 and made a note as follows: "She is definitely myxedematous now and apparently her diabetes is practically gone. Her heart also is behaving well. I believe the thing to do now is to place her on a small ration of thyroid, 1 grain per day. This will not totally abolish her myxedema, but should relieve it considerably and at the same time not be large enough greatly to aggravate her diabetes or cardiac weakness. I should carry on with thyroid alone in order better to evaluate its effect. Later if digitalis seems indicated it can be added."

These directions were carried out. She was placed on a ration of U. S. P. thyroid, 1 grain per day on September 6, after which basal metabolic rate determinations were as follows: September 12,  $-34$ ; September 16,  $-26$ ; September 17,  $-32$ ; September 21,  $-23$ ; September 24,  $-19$ ; and September 29,  $-23$ . She brightened very noticeably during this time and the myxedema facies disappeared. The fasting blood sugar had risen to 169 mg. on October 4, although no glycosuria had appeared. The development of some mild angina pectoris led to the omission of thyroid on October 2, following which the angina disappeared and the basal metabolic rate dropped back to  $-29$  on October 7.

On October 10 thyroid was resumed in smaller dosage,  $\frac{1}{2}$  grain once daily. She has remained on this dose since and has kept essentially free from the symptoms of myxedema, diabetes or angina.

This case illustrates how two diseases may be inimical, one to the other. I do not mean that each aggravates the other, but that each has the effect of diminishing the intensity of the other. Thus, in this case, the more myxedematous the patient became, the less was she diabetic; and as her myxedema was relieved by thyroid, the more did she become diabetic. Also getting too far away from myxedema occasioned attacks of angina.

It will be recalled that Wilder<sup>9</sup> and Blumgart<sup>10</sup> have produced myxedema artificially as a form of treatment for severe diabetes. In our case nature has done something similar, except that the myxedema antedated the diabetes. The therapeutic problem in such a case is an interesting one, namely, so maneuvering as to steer between the Scylla of myxedema and the Charybdis of diabetes. By the use of a smallish dose of thyroid this was accomplished successfully.

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### TREATMENT OF SCARLET FEVER AND DIPHTHERIA\*

#### SCARLET FEVER

THE treatment of scarlet fever resolves itself primarily into a consideration of serum therapy, the theories of its applicability, and the results obtained from its administration in the course of the disease. The surgical complications which arise in its course will be touched upon only insofar as they concern the physician in attendance. A consideration of the origin and nature of the complications is an essential background for treatment, whether medical or surgical. Unfortunately, our knowledge in this respect is far from being satisfactory; consequently, our ideas must always be subject to rearrangement when theories are not substantiated by clinical experience. This statement applies equally to the medical man and to the surgeon who venture to deal with the problems of scarlet fever.

#### SERUM THERAPY

It is necessary to bear in mind that scarlet fever is an expression of a reaction to the invasion of certain strains of hemolytic streptococci. These strains have two very distinct properties. The first is peculiar to these particular strains, namely, the toxin-producing property. The second is the

\* The author has purposely avoided detailed accounts of cases of scarlet fever and diphtheria because of the wide variety of manifestations exhibited in these diseases, and also because the practitioner who is interested in this subject can easily call to mind from his own experiences cases in which the subject matter of this article applies.

pyogenic or pus-forming property, which is shared by hemolytic streptococci in general.

The toxins of the scarlet fever strains produce the primary inflammation of the fauces, the enanthem on the soft palate, the strawberry tongue, and the rash on the skin. The rash consists of capillary dilation with enlargement of the papillae, and is associated with a tendency to minute hemorrhages according to the grade of toxicity in the individual attacked. These ruptured capillaries are most pronounced in the folds of the axillae and groins. We are justified in the inference that there is coincidental endothelial cell damage along with this process, and that the results of this damage may play a part in the subsequent course of the disease. The symptoms of vomiting and fever accompany the toxemia. In this connection Hektoen<sup>1</sup> has observed that "the toxin of scarlet fever streptococci is something more than erythrogenic" in that in susceptible persons it produces other symptoms than those by which we diagnose the disease. This, in brief, is the picture produced by the toxins of these scarlet fever strains.

It is the isolated toxin, or a combination of these toxins, which serves for the Dick test and immunization purposes, and by which we obtain antitoxin from the horse. While it was hoped that bactericidal and antipyrogenic substances would be obtained in the antisera—especially by means of the Dochez method—clinical experience does not substantiate this to the degree in which our hopes were raised. Consequently the direct effect of antitoxin is confined to neutralization of the toxin. When antitoxin is used early enough, preferably in the first twenty-four hours and not later than forty-eight hours after the onset, the effect is usually dramatic in the relief of the toxic symptoms. On this point almost all experienced authors are agreed. The fever drops, the rash fades, and the throat is improved. In fact, it is a common experience to have these cases so greatly improved the following day that only traces of the disease are apparent. This same thing can be achieved by the administration of convalescent scarlet fever serum or by transfusion from a convalescent scarlet fever donor.

This brings us to an important point in the discussion. During the past fifty years the mortality from scarlet fever has been steadily dropping in America and England. Patients

rarely die from toxemia, but they suffer greatly and die from a wide variety of complications. Therefore, it is to the complications that we must turn our attention. It is in this field that we become aware of our lack of knowledge and the resulting disagreement as to the value of therapeutic measures.

The complications of scarlet fever may be divided into those which are of pyogenic origin such as abscess formation; and those which are not, such as arthritis, glomerulonephritis, and purpura hemorrhagica. Again, they may be divided into those which appear with the eruptive stage and those which take place after the acute symptoms have entirely subsided. Lymphadenitis, otitis media, sinusitis, and purulent rhinitis are common in the eruptive stage; yet they often appear rather suddenly at any time during convalescence. Glomerulonephritis and purpura hemorrhagica, however, are more apt to come on abruptly somewhere around the fourteenth day.

The significance of these two classifications of complications is appreciated by the clinician, although he has no clear explanation in mind as to why otitis media, for instance, can take place at the onset when there is every reason to suppose that it is a direct extension of the throat infection; and why exactly the same type of otitis media can occur in the third week of convalescence when, to all appearances at least, the throat and nose are normal and the patient seems on the high road to recovery. This latent phase in scarlet fever is a most perplexing problem, and has called forth an array of theories, none of which is satisfactory. In fact, I am not at all sure that the origin of the early complications is as simple as we try to make it. I have observed an earache with injection of the drum following each weekly injection of the toxin during immunization. Seiferth<sup>2</sup> goes so far as to say that in every case of scarlet fever, hyperemia of the tympanic cavity takes place in the eruptive stage. However, the possibility which all this implies as to the toxic element in the initial stage of early otitis media does not help us to understand the origin of late otitis media when the toxin, to all appearances, is thoroughly neutralized. Furthermore, otitis media can originate while a patient is experiencing that beneficial effect from the early administration of antitoxin. Thus, while complications can well arise from the direct action of

the toxin alone, they may also arise from the penetrating and pyogenic properties of these streptococci. These latter properties may possibly be indirectly related to endothelial cell damage. The effects of this damage might occur early or late in the disease and would not be influenced by the presence of antitoxin, whether spontaneously or artificially supplied.

The effect of serum therapy on the complications of scarlet fever may be divided into two categories. First, it has no appreciable effect on complications, once these have made an appearance. Second, its early administration is not attended universally with any marked lessening of complications. This statement bears qualification. Antitoxin is not of the same standard potency the world over. In spite of the greatest care in preparation, standardization, and aging, different lots of serum from even the same laboratory vary in their efficacy and in their incidence of serum sickness. Convalescent serum varies greatly in its efficacy, and it is not standardized. If pooled serum is used, the antibodies for the offending strain may be sufficiently diluted by the mixture to be quantitatively ineffective.

While antisera are generally effective in combating toxemia, the divergent results in preventing complications can, at least in part, be attributed to the type of serum used, the dosage, and the method of administration. At the scarlet fever congress in Königsberg in 1928 the great majority expressed the opinion that antisera did not prevent complications.<sup>3</sup> More recently, numerous European and the majority of American and English authors report favorable results in this respect in reasonably large series of cases. Toomey<sup>4</sup> has pointed out that in 4611 serum-treated cases recorded in the literature only 26 per cent were controlled by cases from the same epidemic. Toomey found slightly more complications in his serum-treated cases than in the untreated. Nor is his unfavorable experience unique. Kohn and Josey<sup>5</sup> found intramuscular use of Dochez serum ineffective in preventing complications. Cinca<sup>6</sup> and his coworkers in Roumania, where the disease is still severe, Rolleston<sup>7</sup> in London, and Gabriel<sup>8</sup> in Vienna, where the disease has lost much of its toxicity, give little credit to antitoxin in this respect.

At the Haynes Memorial in an analysis of 10,000 cases of scarlet fever we have compared by two different methods the incidence of complications with and without serum. Using the preserum period as a control, we found 15 per cent more complications than in the period where serum was given. During the serum period about one third received serum, and these showed 5 per cent more complications than those receiving no serum. In the first method, we have to discount the fact that the disease has been growing less severe; in the second, we have to recognize that all the very mild cases received no serum. These two factors make it difficult to evaluate the effect of serum therapy on the incidence of complications, in spite of the very dramatic improvement in the toxic symptoms shown by so many of these serum-treated cases.

On the other hand, Place,<sup>9</sup> Gordon<sup>10</sup> and his coworkers,<sup>11</sup> Stevenson<sup>12</sup> and his coworkers, Craig,<sup>13</sup> Friedemann,<sup>14</sup> Hunt,<sup>15</sup> and Banks<sup>16</sup> have reported decidedly favorable results in preventing complications. Hoyne<sup>17</sup> and Bahov<sup>18</sup> have found convalescent serum definitely effective in preventing complications.

Granting that complications have been materially lessened in the hands of most competent observers, there is still to be considered the disadvantage of serum sickness from antitoxin. Numerous authors have pointed out that the routine use of antitoxin in all cases causes more hours of illness in the mild cases than these would ordinarily suffer if not given serum. Consequently we must weigh the good we expect to accomplish with the possibility of serum sickness. Having had three severe Arthus reactions from scarlet fever antitoxin during the past winter, my enthusiasm has been somewhat dampened. It is difficult to reconcile the remark of Banks<sup>16</sup> that he encountered no serum-sensitive patients in his intravenous series with a later remark in the same article that 3 cases suffered from shock after one lot of serum. Place<sup>9</sup> has seen 125 Arthus reactions from antiscarlet and antitetanus serum. The unbridled enthusiasm of some authors<sup>19, 20</sup> reminds me of my own first impressions.

In talking with others of hospital experience I find a growing tendency to reserve serum therapy for severe cases and to favor convalescent serum. There are two disadvantages in convalescent serum. First, as has already been mentioned, it is not standardized, and it sometimes does not contain enough antibodies for the offending strain. Second, it is not obtainable by the general practitioner, except where there are serum centers, as in Detroit and Chicago. Elsewhere the



general practitioner is at the mercy of those who control the supply.

Lichtenstein<sup>21</sup> reports an interesting analysis of 1000 cases equally divided into antitoxin, convalescent serum, and no serum. He attributes his infrequency of serum sickness to the fact that the Swedish serum is not concentrated. The incidence of complications was only very slightly reduced in both of the sera groups.

It is to be hoped that a marketable product will some day be achieved which can be relied on to prevent complications and not to produce serum sickness. But until this is accomplished, many difficulties will have to be overcome and much more will have to be learned about the nature of scarlet fever pathology.

It is necessary to speak of one more measure, namely, the transfusion of blood from convalescent donors.<sup>22</sup> This has been used successfully in very severe cases on admission to the hospital, especially in those septic cases which do not yield to antitoxin and convalescent serum. Schultz<sup>23</sup> reports a case which did not respond to a full dose of antitoxin but the next day was greatly helped by a 300 cc. transfusion from a convalescent scarlet fever donor. There are other factors in this transfused blood besides antibodies to counteract the toxin. Very large doses of convalescent scarlet fever serum have been used in a variety of streptococcic infections not of scarlet fever origin.<sup>24</sup> It would seem probable that the lucky strikes reported in some of these cases result from those other factors in the blood serum which are quite apart from and probably independent of scarlet fever antitoxin. The use of anti-streptococcic human sera for such cases selected on a titer basis would save convalescent scarlet fever serum for its more specific indications.

While the subject of patents hardly belongs under the head of progress in our knowledge of a disease, it is worthy of mention that the *Dick patent* covering the toxin and the antitoxin is controlled by the Scarlet Fever Committee in Chicago, through which licenses for manufacture and distribution are granted. The Dochez N. Y. 5, as well as all other strains derived from scarlet fever, appears to be embraced by the wording of this patent. The Dochez antitoxin patent is held by the Presbyterian Hospital in New York City. One lawsuit has resulted already over these products, and an unwholesome atmosphere has been created of which the practitioner and bacteriologist are conscious. The Dicks' discovery remains a monumental achievement in

medical science. Their subsequent act of putting a legal fence around it seems to have partially obstructed the view.

### TREATMENT OF COMPLICATIONS

*Cervical adenitis*: the most frequent complication in its mild form. Five per cent of the cases develop large painful glands which subside without suppuration, while another 4 per cent suppurate. Local heat affords relief to one individual, while cold affords some degree of comfort to another. We need not be guided by the idea that cold prevents suppuration or that heat draws it to the surface. Pointing takes place toward an ice bag in the same proportion of cases as it does toward a hot water bottle or a poultice. Deep abscesses should be opened by a surgeon; but in those which point to the surface, it is well to let them point and then to make a small nick and express the pus.

*Purulent rhinitis* is very common in both the early and the late septic conditions. It is also, of course, associated with sinusitis, and as such—when hemolytic streptococci are present—is the most common source of spreading scarlet fever. In this connection Gordon<sup>25</sup> has further established that there is no advantage in the continuation of *quarantine* of uncomplicated cases beyond the usual period because of positive hemolytic streptococcus cultures. *Release cultures* appear to be of value only when purulent discharges are present. Gentleness is essential in any attempts to use drops, sprays, swabs, or suction.

*Otitis media*: incidence 12 per cent. Simple otitis is more frequent than is commonly supposed, but is difficult to differentiate from the onset of the suppurative type. It is not prevented by cod liver oil<sup>26</sup> or carotene.<sup>27</sup> Paracentesis is indicated where there is a severe pain, a bulging drum, or an inadequate opening. In a series of 14,733 cases of scarlet fever Williams<sup>28</sup> found that surgical *mastoiditis* followed in 6.6 per cent where paracentesis was done before rupture, in 7.7 per cent where paracentesis was done after rupture, and in 9.3 per cent where spontaneous rupture took place and no paracentesis was done. From which we can draw our own conclusions as to the value of paracentesis in preventing mastoiditis. Kopetzky<sup>29</sup> says: "It is well recognized that paracentesis does not prevent the development of mastoiditis

... [which] is dependent on the bone structure of the tympanic and mastoid areas and on whether or not the original lesion attacks the epitympanic space." In some cases mastoid destruction goes on very rapidly and operative delay is dangerous. An ear which suppurates profusely for three weeks should be regarded as probably due to a mastoid abscess regardless of fever or mastoid tenderness. An x-ray is of great value here. Operation in these cases saves the hearing, sometimes life, and shortens the period of quarantine. Removal of the tonsils and adenoids may be accomplished during scarlet fever with less danger than is commonly supposed, and often with decided benefit to the patient.

*Sinusitis* may occur with the prodromal symptoms of scarlet fever or at any time in the course of the disease.<sup>30</sup> Early surgical interference is to be avoided. Empyema of the ethmoid sinus may penetrate the orbit and produce redness and edema of the upper lid and push out the eyeball. This condition sometimes subsides of itself, but even in the severe forms, under skillful surgical care the prognosis is good. A frontal sinus abscess may burrow into the subdural space in rare instances.

*Nephritis* in a mild degree is a frequent accompaniment of the eruptive stage. Acute glomerulonephritis, especially of the hemorrhagic type, varies in different epidemics from below 1 to above 12 per cent. It occurs most frequently during the third week in an abrupt manner, and uremia may come on without previous warning in the urine or in the chemical analysis of the blood.<sup>31</sup> Chilling seems to be responsible in a few cases.<sup>32</sup> It was formerly thought that a milk diet prevented nephritis. It is now recognized that the incidence is slightly greater if too much milk is supplied. Nor is it the protein content of the milk which is now accused but the fat, which is thought to impair hepatic function and indirectly favor renal inflammation.<sup>33</sup> Jürgens<sup>34</sup> suggests that potato be avoided because of the potassium content, but the facts are entirely against such an assumption. A mixed diet suited to the age and the presence of fever is all that is required. Milk should not be taken in excess.

Thenebe<sup>34</sup> and his coworkers classify glomerulonephritis as "allergic manifestations." The question immediately arises

as to whether the toxin is allergenic. Hooker<sup>36</sup> informs us that the purified toxin is not known to have allergenic properties; it has not been shown to sensitize the skin. Streptococcal nucleoprotein, on the other hand, has this property. Shall we assume, then, that the initial lesion is a kidney infection? Duval and Hibbard<sup>37</sup> in their animal experiments come to the conclusion that the glomeruli are first affected by the toxin, while the interstitial lesions result from infection. These conclusions, however, are based on animal experiments, and there is no ground for assuming that free toxin in any appreciable amount exists in the third week of convalescence. It is necessary to mention all these ideas in order to show what we do not know about nephritis. When we realize this, we can proceed to treat the nephritis in the usual and accepted manner.

*Endocarditis* (rare).\* Place<sup>39</sup> describes the characteristic heart damage as a benign endocarditis. In recent years he has found this condition in less than 0.1 per cent of his scarlet fever cases, though formerly as high as 0.5 per cent. The diagnosis is based on the usual findings of fever, cardiac murmurs with tachycardia, and changes in the size of the heart, arthritis being a usual accompaniment. He found that it usually appeared in the second or third week, persisted a few weeks, and subsided without further damage. A murmur during diastole, or a murmur replacing a heart sound, or persisting through systole, he considers to be indicative of structural change. While he recognizes that the crippling effect varies as in other forms of endocarditis, he is of the opinion that it is slight as compared with rheumatic fever.

This brings up the point mentioned by White,<sup>40</sup> that it is difficult to determine to what extent scarlet fever is a cause of chronic valvular heart disease, because acute polyarthritis, "apparently rheumatic fever," occurs in about one-half of the scarlet fever cases where endocarditis or pericarditis develop.

Salinger and Leonard<sup>41</sup> refer to the endocarditis of "allergic" origin, but the term is not generally accepted. Stolte,<sup>42</sup> on the other hand, gives us a very practical classification of scarlet fever heart conditions. The first group comprises those

\* Zischinsky<sup>38</sup> found only 10 among 20,000 hospital cases of scarlet fever in Vienna.

benign conditions which Place has described; the second, those with arthritis, pericarditis, and the sweating so characteristic of rheumatic fever; the third, malignant endocarditis. In the first group, rest in bed is, of course, essential, but no medicinal treatment is indicated. 'Salicylates are helpful in the second group. Transfusions may be tried in the malignant type. The usual indications for digitalis are rarely present in the acute stage; and when they are present, pericarditis or septicemia is apt to interfere with any good that may be accomplished.

*Purpura hemorrhagica* (rare) may occur in a mild form early, but in its severe, abrupt, and fulminating form appears about the fourteenth day. The purpura may appear only on the lower part of the legs or arms. Again, it may suddenly involve the entire cutaneous surface and the mucous membranes, with a fatal outcome within forty-eight hours of its onset. Like acute glomerulonephritis, it appears to have no relation to the severity of the initial scarlet fever rash. Furthermore, it bears no relation to a previous history or family history of a purpuric diathesis.<sup>48</sup> Box<sup>49</sup> considers this complication to be due to a supersensitive stage in the course of establishing immunity. We might well speculate on its origin from the results of endothelial cell damage in the eruptive stage. In severe cases transfusion is indicated, and a convalescent scarlet fever donor may be used.

*Appendicitis* (rare). When this occurs in scarlet fever it is apt to be of the abrupt and fulminating type. Any delay in calling in surgical aid may result in rupture and peritonitis. If the appendix has not ruptured, a drain should not be used, as the wound will then surely slough wide open later. The wound should be closed tight, as in any clean case, even if the rash is in full bloom. There is a strong tendency for clean wounds, such as in a hernia operation, to slough wide open if scarlet fever supervenes on the operation. We have found that closing tight an unruptured appendectomy wound affords a very good chance of primary healing. It should be the duty of the attending physician to bring this forcibly to the attention of the surgeon called in.

*Empyema* (rare). When this develops in the course of scarlet fever, the closed method, even in adults, has been

found to be the safest initial surgical procedure, even though it sometimes has to be followed by a rib resection. One or more tappings may be advisable to favor the walling-off process. Allowing a large amount of serum to accumulate is to be avoided. The determination of the presence of empyema in scarlet fever does not demand the haste of surgical intervention as in appendicitis.

The initial responsibility in all these surgical complications rests with the attending physician. He must learn to recognize their importance, and through his knowledge of scarlet fever he should continue to be an active adviser to the surgeon throughout the case.

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## DIPHTHERIA

### SERUM THERAPY IN MILD AND MALIGNANT DIPHTHERIA

Recent advances in our knowledge regarding the serum treatment of diphtheria deal with the size of the dose and the methods of administration. The prevalence of the malignant type of the disease in Austria, Germany, Scandinavia and England has stimulated a lively interest in this subject. These malignant cases occur sporadically in America, and their relatively poor response to vigorous antitoxin therapy has caused consternation abroad even to the point of downright skepticism as regards the value of this agent. To my mind, this attitude is wrong. Recognition of the possibility of the severe type should prompt us to avoid any unnecessary delay in treatment, instead of permitting us to adopt the nihilism emanating from Vienna (Zischinsky).<sup>1</sup>

The mechanism of antitoxin therapy is essentially a protective or preventive one. If the clinician grasps the fact that the curative virtue of antitoxin is based on its protective value, he will not allow himself to become confused by the recent unfavorable reports of antitoxin therapy in this disease, or by the divergent opinions regarding dosage and methods of administration.

Let us start with the undeniable fact that antitoxin is as capable of neutralizing the toxin as water is capable of putting out a fire. The basis for this statement lies in the very method by which a unit of antitoxin is standardized. But here we are immediately confronted by the statement of Friedberger<sup>2</sup> that the natural diphtheria in man is as different from the toxin diphtheria in the guinea-pig as a man is from a guinea-pig. We admit the logic of this only to a certain extent. We are well aware that barriers of resistance exist in the mucous membranes of the upper respiratory tract of man which delay invasion and tend to prevent absorption of the toxin. These barriers, however, which vary so greatly in different individuals, may actually augment the danger because they are the cause of delays in recognition of the disease. This may



sound paradoxical, but it is not. A smouldering fire is potentially capable of bursting into flame. Diphtheria may smoulder, so to speak, and go out of itself, or it may take on a malignant aspect at the very start or after a period in which these barriers have tended to hold back the disease process. The amount of antitoxin necessary to neutralize the toxin in a given case depends on whether the process is being held at bay, and on whether a malignant aspect is manifest, and if so, how far it has proceeded.

In neutralizing the toxin in the guinea-pig, the antitoxin is usually given simultaneously. A dose which will save a guinea-pig if administered within fifteen minutes of the toxin will not suffice if given later. In fact, if we wait two hours and a quarter, a dose one thousand times as great will not suffice to save the animal.<sup>3</sup> When we realize that 1000 units of antitoxin to a guinea-pig corresponds to 100,000 units for a 50-pound child, we can easily understand why enormous doses of antitoxin so often fail to save malignant cases. The appreciation of these facts shows the difference as well as the relationship of experimental toxin diphtheria in the guinea-pig and the natural disease in man. It emphasizes the important part that time plays in the protective action of antitoxin.

It thus becomes obvious that the time element in conjunction with the stage of the disease process constitutes the basis for gauging the dose of antitoxin. Furthermore, we must bear in mind that antitoxin therapy is essentially protective. It does not dissolve the membrane. It does not destroy the bacilli. What it does is to neutralize the toxin, and thus, by protecting the tissues, it allows the operation of those other natural forces of the tissues, so vitally concerned with the recovery of the patient.

With these facts in mind we can understand why the question of the required dosage in cases of diphtheria cannot be met with definite answers. You might as well ask the chief of the fire department how much water on the average he needs to put out a fire. You know perfectly well that a pail of water will be enough at the start, but once it gets under way the answer becomes involved. If the house burns down, one does not say that water doesn't put out fire. This may

all seem so elementary as to appear entirely unnecessary. But when clinicians in posts of authority are voicing their disbelief in antitoxin as a result of their experiences with malignant diphtheria, it is time to revert to first principles.

Dosage, then, is dependent on the time element. It also depends on the manner of administration. The intravenous route gives us the most prompt action, but two-thirds of the antitoxin so given leaves the blood within twenty-four hours.<sup>4</sup> Thus, if conditions warrant this method of approach, it is desirable to inject another dose into the gluteus muscle, from which site it will be continually given off, reaching its maximum concentration in the blood at the end of twenty-four hours. The subcutaneous route is the slowest.

Park<sup>5</sup> in New York advocates a scale of dosage which varies from 3000 to 60,000 units. In Boston we have been accustomed to employ approximately twice as much. Recent accounts from Paris,<sup>6</sup> where the intramuscular and subcutaneous routes are used, advocate a scale running from 45,000 to 300,000 units. Bie<sup>7</sup> in Copenhagen has given as much as 500,000 units. Bie influenced many of us by his high scale of dosage, which was accompanied by an extraordinarily low death rate; but this was before the wave of malignant cases, which, in spite of this high dosage, has brought about a high death rate.<sup>8</sup> In Stockholm a high dosage scale was carried out from 1925 to 1928, but on analyzing the results Lichtenstein<sup>9</sup> found that the mortality in the severe uncomplicated faucial type remained the same as it had been over a previous period with much smaller doses.

From these hospital statistics we are confronted with the fact that the routine use of the larger doses shows no apparent advantage as determined by the yearly mortality and the incidence of postdiphtheritic paralysis. In other words, our attempts to protect well advanced severe cases have perhaps carried us beyond the maximal dose which could be effective. We must not lose sight of the fact that hospital mortalities are dependent on the promptness with which outside physicians recognize diphtheria. This applies not only to the above-mentioned smouldering type, but more particularly to the malignant type, where the time element becomes such a crucial factor.

From the point of view of the clinician the malignant type offers no new problem. It has been constantly with us in the sporadic form. Its increase would appear to result from unknown environmental conditions affecting man's resistance. It is not a new disease but a virulent form of the same one, occurring in parts of Europe as 10 per cent of the diphtheria cases. In Berlin the death rate in this type has been as high as 50 per cent.<sup>8</sup> Bacteriologically it represents a virulent strain with increased penetrating and increased toxin-producing properties. So fulminating is it at its worst that large doses given during the first twenty-four hours have proved ineffective. I have seen one case referred to us by one of my former interns who gave all the available antitoxin (30,000 units) before sending it to the hospital, where the child received 130,000 more units but died within thirty-six hours of the onset. No one was to blame. Antitoxin was simply ineffective because it could not protect against this overwhelming infection. To say that the antitoxin was ineffective as a protection by no means implies that it was inert. Animal experiments with these new strains give unsatisfactory results because animals may react more unfavorably to the milder strains than to the malignant strains.<sup>10</sup> To suggest that malignant types are due to mixed infections with a streptococcus<sup>4</sup> is to sidestep the issue. The streptococcus is found also in the blood of malignant smallpox cases. Where antistreptococcic sera have been used in conjunction with antitoxin the mortality was 55 per cent.<sup>3</sup> It is true that a mixture of scarlet fever and diphtheria was an ugly combination before the days of antitoxin, but it is no longer so formidable. If an antitoxin derived from a malignant strain<sup>11</sup> proves more effective clinically in these cases, we shall still be confronted with the time element of its administration. Since the regular antitoxin is capable of neutralizing the toxin of the malignant strains, every effort should be used to apply it early. In these cases it does not depend on the day of the disease but on the hour.

Another factor which has come to light in recent literature tends to bring us back to first principles, and also suggests that we may be overstepping the mark in dosage. In 1918 Bingel<sup>12</sup> gave us a surprise when he found that cases

treated with "normal" horse serum did as well as those given equal doses of antitoxin. He later informed us that the "normal" serum was obtained from horses used for antitoxin purposes in which the antitoxin titer had fallen to a very low level. Recently Hottinger and Toepfer<sup>8</sup> have concluded that they have reduced the mortality of malignant cases in their hospital in Düsseldorf from 43.5 per cent to 17.0 per cent (not including those moribund on admission) by giving 4000 units intravenously and repeating this dose intramuscularly two to four times a day with interspersed doses of this low titer antitoxin. Naturally, the idea of nonspecific protein therapy was brought forward as an explanation of these results. It has remained for von Bormann<sup>3</sup> to establish the fact that nonspecific protein therapy is not concerned with the results recorded by Bingel, Hottinger and Toepfer. By injecting various strains of diphtheria bacilli into the conjunctival sacs of guinea-pigs he has tested the relative efficacy of these three sera. With antitoxin the animal is saved, and sometimes the eye is not damaged. With low titer antitoxin the animal is sometimes saved, but the eye is lost. With really normal horse serum there is a 100 per cent mortality. Over 300 animals were used. Since the guinea-pig may be protected by serum with a very low antitoxin content, he argues that the use of the original method of giving 1000 to 2000 units in mild cases—doses with which antitoxin won its first laurels—is not so far wrong as we have come to think.

In other words, recent laboratory and clinical results suggest that the mild cases may be sufficiently protected by doses of 500 to 1000 units, that malignant cases, if treated early, may often be protected by frequently repeated doses of 4000 units, and that a certain number of malignant cases reach us too late to be saved from a fatal outcome by any amount of antitoxin. With this in mind, one is inclined to play safe by allowing plenty of margin in the milder cases and to persevere vigorously in the malignant ones with the hope that treatment may have been begun in time.

Thus the practitioners whom we were wont to accuse of giving inadequate doses may derive some satisfaction from the new light on this subject, while others like myself are prompted to recede cautiously from the maximal doses we

have been in the habit of using. The theory that one large enough single dose at the beginning should be our aim, as advocated by Park and Schick, still applies to the mild types, and Park's dosage scale appears to be vindicated. The frequent repetition of small or moderate doses in malignant cases would seem to be worthy of trial. Roughly speaking, the minimal dose is 3000 units subcutaneously. The maximal dosage is 500,000 units given intravenously and intramuscularly in repeated daily doses averaging 100,000 units. While any scale of dosage is unsatisfactory because it is incomplete, the following is a rough guide to be varied by the duration of the symptoms and their severity.

DOSAGE OF ANTITOXIN IN UNITS

Weight of patient.	Mild.	Moderate.	Malignant.
Under 50 lbs.	5,000	10,000	50,000
Over 50 lbs.	10,000	20,000	100,000

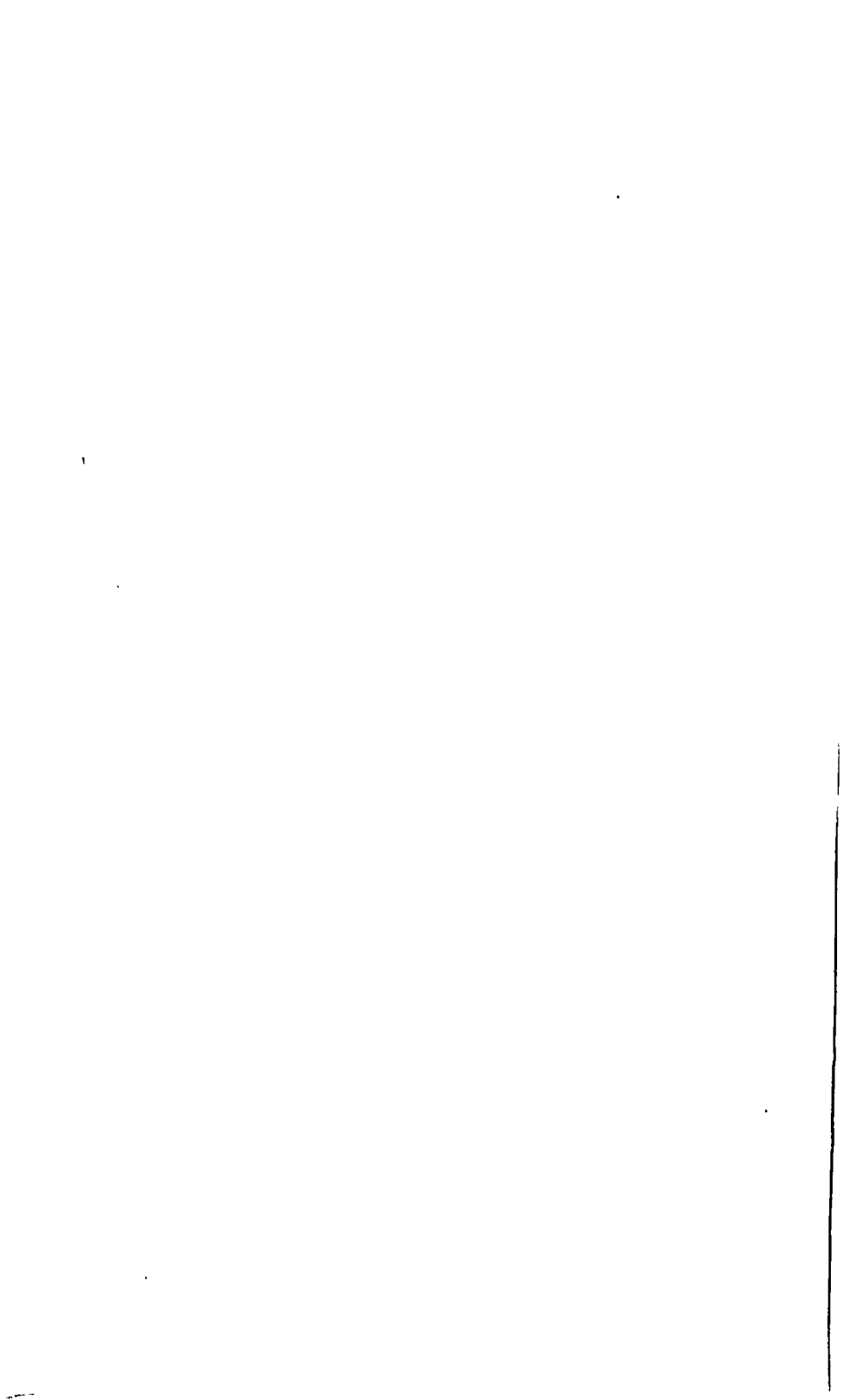
Antitoxin should not be used in the postdiphtheritic paralyses; first, because it does no good; second, because there is ample antitoxin in blood at this stage; and third, because of the danger of anaphylactic shock eight to nine days after the first dose.

While the protection which antitoxin affords to man is not to be compared to the protection afforded by active immunization, we must keep in mind that the early bedside recognition of diphtheria governs the amount of antitoxin required.

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### SOME RECENT ADVANCES IN VACCINES AND SERUMS: A. REVIEW

#### INTRODUCTION

IT is manifestly impossible in this communication to discuss completely all the topics which this title might suggest. It seems wiser, therefore, to limit this review to those topics which are relatively new and which are receiving considerable attention from the medical profession at the present time. The writer intends to express freely his own opinions of the relative merits of these several biological products. The topics which will be reviewed are: (*a*) whooping cough vaccine; (*b*) placental extract; (*c*) tetanus toxoid; (*d*) meningococcus antitoxin (Ferry); (*e*) staphylococcus toxoid, and (*f*) staphylococcus antitoxin.

#### WHOOPIING COUGH VACCINE

During the past few years two new products have received considerable attention for the prophylaxis of whooping cough. Furthermore, a few papers have appeared in recent years suggesting that a filtrable virus plays an etiological rôle in the disease. Since the etiological rôle of an organism in any disease should be definitely established before it is justifiable to use that organism in a prophylactic vaccine it will be well briefly to review the etiology of whooping cough.

Ever since hemophilus pertussis was first described by Bordet and Gengou<sup>1</sup> as the causative agent of whooping cough, occasional reports have appeared purporting to cast doubt on



the etiological rôle of this bacterium and suggesting that a virus may be a factor in the cause of the disease. The various arguments in favor of the virus theory have recently been summarized by Rich<sup>2</sup> as follows: (*a*) pertussis bronchopneumonia is an interstitial reaction, with mononuclear cells predominating, which is the characteristic type of histopathological response to virus infection; (*b*) pertussis results in a permanent immunity as in most virus diseases, whereas most bacterial diseases do not (Note: we might point out that several virus diseases are characterized by a very short immunity, *i. e.*, herpes labialis, the common cold, and influenza, and that prolonged immunity is supposed to follow some bacterial infections such as typhoid, cholera, plague, etc.); (*c*) *Hemophilus pertussis* is isolated only during the early stages of the disease; (*d*) intranuclear inclusion bodies have been described as occurring in the lungs of children dying of pertussis bronchopneumonia; (*e*) experimental transmission of the disease (Rich, 1932) has not been adequately demonstrated and thus Koch's postulates are not fulfilled.

Recently, Sprunt, Martin and Williams<sup>3, 4</sup> have answered the argument of Rich that the mononuclear interstitial reaction in the lungs suggests a virus etiology. These investigators produced this type of reaction in the lungs of rabbits by the intratracheal injection of pure cultures of Bordet-Gengou bacilli. A similar bronchopneumonia was produced with the typhoid bacillus. Furthermore, the same type of reaction was produced by the intratracheal injection of various bacterial toxins (*staphylococcus aureus*, hemolytic streptococcus and diphtheria toxins). These authors found that these reactions could not be differentiated from that occurring in children dying of pertussis bronchopneumonia or from that caused in animals by the viruses of epidemic influenza and psittacosis.

Within the past few years McCordock,<sup>5</sup> Rich<sup>2</sup> and McCordock and Smith<sup>6</sup> have demonstrated intranuclear inclusion bodies in the lungs of children dying of pertussis, which they feel suggests the possibility that a virus may be the primary etiological agent. Rich does suggest that these inclusion bodies might be due to aspirated herpes virus. McCordock also reviews a few instances from the literature where similar

bodies were found in nonpertussis patients. Furthermore, the inclusion bodies described by Farber and Wolbach<sup>7</sup> as occurring in the salivary glands of a considerable percentage of infants dying from a variety of causes are morphologically indistinguishable from the inclusion bodies described by the above authors in the lungs of patients with pertussis.

Because of these suggestions that a virus may play a rôle in the etiology of whooping cough some recent transmission experiments have been done which, in our opinion, offer very conclusive proof that *Hemophilus pertussis* is the sole etiological agent in this disease. It should be pointed out that in regard to the old transmission experiments cited by Rich<sup>2</sup> the dissociation of *Hemophilus pertussis* was not understood. At the time when these investigations were done it is likely that some of these experiments were carried out with avirulent strains.

Sauer<sup>8</sup> inoculated (into the nose and throat) healthy young Rhesus and Ringtail monkeys with virulent Phase I cultures. In 8 out of 76 instances the animals developed a paroxysmal cough followed by vomiting of mucus after an incubation period of seven to twenty days. The organism recovered from one coughing animal produced the disease in another animal inoculated with it. This, of course, is not an entirely convincing experiment because of the very small percentage of positive results. In 1933, Macdonald and Macdonald<sup>9</sup> reported a unique experiment on human volunteers. Four healthy boys whose medical histories were accurately known were used in these observations. Two of the boys had been vaccinated two months previously with the Sauer vaccine. The other two were nonimmune. The throats of all four were sprayed with the filtrate of the first generation of a freshly isolated culture. No symptoms developed. The boys were kept rigidly quarantined in a country camp. Eighteen days later a suspension containing 140 bacilli was dropped into the nose and throat of each boy. The nonimmune boys developed typical whooping cough with positive cough plates. The vaccinated boys remained free of symptoms and had no positive cough plates even though they were all kept together throughout the period of observation. These authors conclude that the Bordet-Gengou bacillus is the sole cause of whooping

cough and that active immunity is conferred by the injection of *Hemophilus pertussis* vaccine.

In Shibley's<sup>10</sup> more recent transmission experiment the virus possibility was examined still further. This author carried a Phase I culture through 60 generations in order to be certain that a virus was not carried over in the culture. With this culture he succeeded in producing a typical train of symptoms in a chimpanzee. The animal was sacrificed and *Hemophilus pertussis* was recovered from various locations in the respiratory tract.

We have not reviewed the additional positive evidence pointing to *Hemophilus pertussis* as the sole etiological agent of whooping cough. We merely desired to point out the inadequacy of the virus theory of etiology. In our opinion the evidence points conclusively to *Hemophilus pertussis* as the sole cause of the disease.

Within the past few years there has been considerable advance in our knowledge of the biology and antigenic composition of the Bordet-Gengou bacillus which has an extremely important bearing on prophylaxis by vaccination. Lawson<sup>11</sup> and Leslie and Gardner<sup>12</sup> have shown that *Hemophilus pertussis* is capable of undergoing dissociation into serologically different variants, which have been termed Phases I, II, III and IV. Each of these phases probably possesses a different antigenic structure. The serological differences between these mutation forms probably accounts for the several types of pertussis bacilli described in the older literature. As far as we know now *Hemophilus pertussis* is a homogeneous species. Phase I is always hemolytic and is the form recovered in the disease. It is the virulent phase and corresponds to the "smooth" form in general dissociation nomenclature. Phases III and IV are "rough" or avirulent. The importance of this is that if any prophylactic vaccine is to be of value it must be made from Phase I cultures.

Innumerable attempts have been made in the past to actively immunize children with hemophilus pertussis vaccines. Such attempts have been almost uniformly unsuccessful. Even Madsen's<sup>13</sup> unique experiences in the Faroe Islands are not entirely convincing. It is of some interest that in 1931 the Council on Pharmacy and Chemistry of the American

Medical Association removed pertussis vaccines from New and Nonofficial Remedies because there was no convincing evidence as to their value either prophylactically or therapeutically. In light of our present knowledge there are several possible reasons for the failure of these vaccines. Many of such vaccines were probably made from dissociated, avirulent cultures. Immunization generally was not done a sufficiently long time before exposure (in fact, in most instances such vaccines were administered either after exposure or during the early stages of the disease). Also the immunizing doses used were probably entirely too small.

In a series of communications during the past few years. Sauer<sup>14, 15, 16, 17</sup> has described his experiences with his new type of whooping cough vaccine. His vaccine is prepared and administered in such a manner that the probable reasons for failure of the older vaccines are overcome.

Sauer's method of preparing and administering his vaccine is as follows. We quote excerpts from his papers directly. "Bacillus pertussis vaccine (1 cc. = 10 billion bacilli), is made from recently isolated, strongly hemolytic (Phase I) strains, grown on Bordet (potato-glycerin extract agar) medium made with freshly defibrinated human blood. To minimize the culture medium content, the forty-eight hour growth is scraped off and mixed with 0.5 per cent phenolized physiologic solution of sodium chloride. To insure purity, a stained smear of each surface growth is examined before it is harvested. After a week in the refrigerator (during which time it is shaken daily), the concentrated suspension is cultured for sterility on three successive days. After dilution with 0.5 per cent phenolized physiologic solution of sodium chloride so that 1 cc. contains about 10 billion bacilli, it is tubed, sealed and refrigerated until shortly before it is used."

Sauer has emphasized several essential points concerning the production of this vaccine which can be reiterated with profit. It should be made with freshly isolated, Phase I cultures. It is made with human blood medium because: (a) the organism is more apt to be maintained in its virulent phase on this medium; (b) foreign blood protein from the medium cannot be taken up with the vaccine. This eliminates any possibility of sensitization and subsequent hypersensitive reaction.

We feel that it is probably not essential to use human blood. So far as we know the organism will maintain its original antigenic structure on sheep or other blood as well as on human blood. The vaccine is not heat killed, which eliminates any possibility of antigenic change or reduction of antigenic potency due to heat denaturation, etc.

A total of 8 cc. or 80 billion bacilli are given in three bilateral injections at weekly intervals. They are given subcutaneously in the deltoid and triceps regions. Subsequent injections should not be given in the same spot as the preceding in order to avoid the possibility of a local reaction. Care should also be exercised that the injections are not given intravenously. The first injection consists of 1 cc. in each arm; 1.5 cc. being given in each arm at the second and third injections.

Sauer's experiences with reactions following these injections are as follows: "The local and systemic reactions are due to the vaccine (dead bacilli and endotoxin), and not to the phenol or medium proteins . . . Allergic reactions, sensitization to foreign protein and susceptibility to the Arthus phenomenon need not be feared, regardless of the amount of vaccine injected or the time interval between injections. . . . If a severe reaction follows an injection, the next injection may be postponed a few days, or only 1 cc. may be given (bilaterally) at subsequent injections and an extra one given a week after the third injection. The parents are forewarned of a transient rise in temperature, the temporary local reactions (redness, induration and tenderness) and the subcutaneous nodules, which may persist for a few weeks at the site of each injection."

Since the first three years of life constitute the danger period in whooping cough mortality, prophylactic vaccination should preferably be done during infancy. Sauer recommends that it be done during the second half of the first year of life. It would also be advisable to immunize older, nonimmune children who have some chronic or debilitating disease such as tuberculosis, asthma, chronic pulmonary suppuration, etc.

One extremely important point emphasized by Sauer is that whooping cough vaccine is of no value unless *it is given at least a month or longer before exposure. It is of no value*

*if given after exposure or during the catarrhal stage and is of no therapeutic value at any time during the course of the disease.* This, of course, is in keeping with the general immunological principles governing active immunization in any acute disease.

Sauer has published very convincing evidence, obtained from well-controlled studies, as to the effectiveness of whooping cough vaccine. In one of his studies he was able to vaccinate certain children in individual families and leave the others as controls. During the course of five years 31 of such control children in 24 families developed whooping cough, whereas; 29 vaccinated children in these same families who were intimately exposed during the incubation, catarrhal and paroxysmal stages, failed to develop the disease. During the same period 162 vaccinated children who were accidentally exposed failed to develop the disease. We have already quoted, in our discussion on etiology, the experiences of Macdonald and Macdonald, which are excellent evidence for the effectiveness of prophylactic vaccination. Recently, Sauer<sup>18</sup> has described a few failures of his prophylactic vaccination.

During the past few years Krueger<sup>19, 20, 21</sup> and his associates have described their method for the production of a so-called "pertussis" undenatured endo-antigen. We quote freely the description of their method. Phase I organisms are harvested in buffered, isotonic solution, thoroughly washed to remove metabolites and then mechanically disrupted by grinding for twelve hours in a special type of ball mill. The resultant suspension is subjected to ultrafiltration through acetic collodion membranes of such porosity that all intact cells are retained while material in solution or in a finely dispersed phase passes through. The *water-clear* filtrate contains those constituents of the live cell put into solution or suspension by physical rupture of the cell membrane. Each cubic centimeter contains the extract from 12 billion organisms.

We feel that there is insufficient evidence available to justify the assumption that this is a better immunizing agent than the vaccine prepared of whole organisms according to Sauer's method. Grinding will undoubtedly produce a suspension of smaller particles, however, the bulk of substance will probably be in physical suspension rather than in true chemical

solution. Under these circumstances the method of ultrafiltration which results in a "water-clear solution" will undoubtedly remove considerable immunizing substance. Furthermore, the method makes it difficult to quantitate dosage in terms of the amount of original substance. Recently an attempt has been made to standardize this product by nitrogen determinations. Krueger's main claim is that his antigen is "undenatured" because it has not been heated. We might point out again that Sauer's vaccine is *not heated*—in fact, it is subjected to much less physical manipulation than is Krueger's endo-antigen.

Miller<sup>22</sup> has reported results in rabbits suggesting that Krueger's extract is better than other immunizing preparations. He determined this by means of complement fixation which, in our opinion, is not especially reliable for a quantitative study of the development of active immunity. Rabbits are poor animals for the study of such a problem since they are not susceptible to *Hemophilus pertussis* infection, or rather, they are naturally immune to it.

Frawley and his associates,<sup>23</sup> Stallings and Nichols,<sup>24</sup> and Munns and Aldrich<sup>25</sup> have reported results on the therapeutic use of Krueger's antigen in which they claim definite benefit from it. They do not seem to us to have proved this claim. In view of Sauer's experience that whooping cough vaccine is of no value in treating the disease (and this is the experience in other well-controlled observations) we see no reason why Krueger's antigen should have any therapeutic value at least insofar as such therapeutic value is dependent upon the development of an active immunity. Frawley<sup>26</sup> used this antigen prophylactically, and found that he did not get complete protection, although he states that the disease was milder. This experience, it seems to us, is further proof that this antigen is of no therapeutic value when given during the course of the disease. It is always difficult to appraise, even after careful questioning, the statements of a solicitous mother regarding the effect on her child of an "injection for his whooping cough." We feel that there is no justification for the use of any pertussis antigen or vaccine as a *therapeutic* agent.

In summary, it seems to us the evidence so far advanced indicates that whooping cough vaccine, as Sauer has prepared

it, represents a prophylactic *active immunizing* agent. We feel that its use is justified for this purpose only. Nevertheless, the experience with it is not yet sufficiently large to permit its acceptance without reservation or doubt. When it is used in a child the parents should be given no guarantee as to the result. It should not be forgotten that whooping cough is a protean disease and its contagiousness is not great compared to other communicable diseases. In fact, a considerable percentage of individuals reach adult life without contracting the disease.

Sauer's studies are still too recent to show how long the immunity will last following vaccination. It would appear that it will last longer than the danger period for pertussis mortality. Sauer has some children who have been exposed from five to eight years after vaccination without developing the disease.

#### PLACENTAL EXTRACT (McKHANN)

McKhann and his associates<sup>27, 28, 29, 30</sup> have prepared an extract from human placentas which is capable of preventing or modifying measles in exposed, nonimmune children. That immune bodies might be derived from placentas and their blood content was suggested by the fact that: newborn infants are immune, for a period of several months, to certain communicable diseases: diphtheria antitoxin is present in essentially equivalent amounts in umbilical cord blood and in maternal blood. Furthermore, transplacental transfer of certain antibodies has been definitely shown to occur. This question of transplacental transmission has been reviewed in detail by McKhann and Chu in their first paper.

We quote McKhann's most recent technic for preparing placental extract, as follows: "Normal-appearing placentas from nonsyphilitic and nontoxic mothers were collected in lots containing from 8 to 50 placentas. The umbilical cords were tied to prevent loss of the fetal blood contained in the organs . . . the organs were ground very fine in a food chopper. Extraction was carried out with 4 per cent salt solution. Hypertonic saline was used in order to minimize hemolysis, which occurs rapidly in umbilical cord blood and in the placental extract prepared in isotonic salt solution. About



300 cc. of the salt solution was added for each placenta. The material was stirred mechanically for half an hour, and at the end of this time the tissue debris was removed by filtration through cheesecloth after which the blood cells were removed by centrifugation. Extraction of each lot was repeated once or twice so that the total amount of saline used was from 750 to 1000 cc. per placenta.

"Such extracts contained fetal blood, some maternal blood, and a quantity of placental tissue protein. Because of the association of immune bodies with the globulins of the blood serum of lower animals and presumably of human beings a concentrate of the active material and the removal of inert or noxious matter was sought by separation of the globulin fractions through precipitation with ammonium sulphate. Tests for toxicity and sex hormones indicated that the globulins contained a negligible amount of the hormones and that they were nontoxic for animals even if injected in large doses. Also, by animal tests and clinical trial the antibodies sought were found to be present in the globulin fractions."

Further differential precipitations were carried out at different concentrations of ammonium sulphate. The ammonium sulphate was removed by dialyzing in cellophane tubes against running water and isotonic salt solution. The material was preserved and sterilized by adding merthiolate 1:5000 or by passage through a Berkefeld filter.

In general it has been found that placental extracts are capable of: (1) neutralizing diphtheria toxin, (2) blanching a scarlet fever rash, (3) neutralizing poliomyelitis virus, and (4) preventing or modifying measles.

In their most recent paper McKhann, Green and Coady have presented the results obtained by studying the several protein fractions of placental extract as well as the total result of their experiences in the prevention and modification of measles with these substances. It was found that the substance neutralizing diphtheria toxin was found almost entirely in the pseudoglobulin fraction. The substance responsible for blanching scarlet fever rashes was also found almost exclusively in this same fraction. It was shown that injections of placental extract subcutaneously or intramuscularly in patients with a positive Dick reaction were followed by a period of

several days during which Dick tests were negative. This same observation was made independently by Ross.<sup>31</sup>

This striking protein distribution was not present in the case of antibodies for virus diseases, that is, for measles and poliomyelitis. In these instances the antibodies were distributed about equally between three fractions; the pseudoglobulin, the euglobulin and the tissue proteins.

These authors have presented data describing the use of placental extract for the prevention or modification of measles in 1285 nonimmune children. The several protein fractions were used. In one group of 560 children who were intimately exposed (under circumstances such that one would expect an infection rate of some 90 per cent) measles was either modified or prevented in 93 per cent.

With regard to reactions following the injection of placental extract in this large group of patients it was found . . . "that 23 per cent of the patients had mild local reactions and that 12 per cent had a slight general reaction as indicated by fever. The incidence of severe local reactions was 2.8 per cent and of more severe febrile reactions (indicated by an elevation of temperature over 101° F.), 1.9 per cent. In no instance did a local reaction persist longer than four days, and in no instance did suppuration occur." Reactions were more frequent among older children and adults than among infants and young children. Placental extract was found not to sensitize patients to subsequent injections of this material.

There appears to be no question but that placental extract is capable of preventing or modifying measles and should, therefore, be a valuable agent in the control of this disease. There is no reason to suppose that the activity of placental extract is due to substances different from those contained in convalescent serum. Its greatest merit would seem to be that an adequate supply of the material can always be available. It should do away with the trouble and annoyance of seeking and obtaining convalescent serum at just the right moment when occasion for its use arises.

As McKhann has pointed out, the immunity conferred by an injection of placental extract is passive and therefore of short duration. For this reason it is probably best not to use it for protection except in institutions and in debilitated,

tuberculous, acutely or chronically ill children. Its greatest value should be in its use as an agent to cause modified or mild measles. It is probable that under these circumstances permanent immunity against measles would result. McKhann has also pointed out that it is necessary to improve the product further to remove substances which might cause reactions and that some method of more certain and uniform standardization is very desirable. In the use of this extract it is most important that potent products, so prepared as to lessen the possibility of reactions, should be obtained.

#### TETANUS TOXOID

During the past few years tetanus toxoid has been developed and this product bids fair to supplant the older methods of prophylaxis against tetanus infection.

In 1924 and 1925 Ramon<sup>32, 33, 34</sup> published his classical studies on rendering diphtheria toxin nontoxic by treating it for several weeks at 37° C. with 0.4 per cent formaldehyde. At about the same time Descomby<sup>35</sup> found that tetanus toxin could be rendered nontoxic by treating it in the same way. This product, toxoid, retained its antigenic properties in spite of the loss of toxicity, and thus offered a method for active immunization against tetanus.

Tetanus toxoid is prepared by the addition of 0.3 to 0.4 per cent formaldehyde to tetanus toxin and incubating the mixture at 37° C. for several weeks. The end-point of the period of incubation is determined by the loss of toxicity of the material for laboratory animals. By such treatment a toxin with an M.L.D. of 0.001 to 0.0001 cc. can be so reduced in toxicity that 10 cc. will fail to kill a guinea pig. Such toxins are considered to be adequately changed to toxoid when 5 cc. to 10 cc. fail to cause symptoms of tetanus when injected into a guinea pig. Bergey<sup>36</sup> and others have shown that the best toxoid is derived from the most potent original toxin.

There have been a number of studies on the production of antitoxin in human beings and animals following two or three injections of toxoid at biweekly or triweekly intervals. Such studies have been published by Ramon and Zoeller,<sup>37, 38</sup> Sacquépée,<sup>39</sup> Lincoln and Greenwald,<sup>40</sup> Sneath,<sup>41, 42, 43</sup> Bergey

and Etris<sup>44, 45, 46</sup> and Bergey.<sup>36</sup> Ramon<sup>47</sup> has recently published a review of this entire subject. In general these studies have shown that the rise in antitoxin following the primary stimulus is rather slow, reaching a maximum in from three to five months. After this interval of time in persons receiving two or three injections of toxoid the antitoxin level in the serum averages about that occasioned by the injection of the usual prophylactic dose of antitoxin. However, in a large group of immunized individuals, there will be considerable variation in the level of antitoxin in their serum. This immunity apparently lasts for a considerable period of time. The serum antitoxin level apparently maintains itself for twelve to eighteen months and then slowly begins to fall. Ramon and Zoeller<sup>48</sup> injected a large group of individuals with tetanus toxoid and in some of them the serum antitoxin level following this varied from 0.5 to 1 unit per cc. Four years later 12 of these individuals had serum antitoxin contents of from  $\frac{1}{500}$  to  $\frac{1}{6}$  unit per cc.

It has also been shown that a secondary stimulus (an injection of toxoid in a person immunized some time previously) is followed by a very rapid rise in antitoxin to a new high level. Such a secondary stimulus is followed, in from seven to fifteen days, by a rise in antitoxin which may be several hundred times greater than the antitoxin level just prior to the secondary stimulus. In fact the level attained after such a stimulus is usually many times higher than the optimum level following the primary stimulus. The importance of this will be discussed later.

Recently, Bergey<sup>36</sup> has shown that tetanus toxoid can be precipitated with 2 per cent alum. When washed according to the method of Wells, Graham and Havens<sup>49</sup> this purified alum toxoid was not followed by the annoying reactions which sometimes followed the use of nonprecipitated toxoid. Because alum toxoid is retained longer in the tissues it acts as an antigenic stimulus for a much longer time than regular toxoid. A single dose of alum toxoid is followed by an antitoxin content similar to that following three injections of regular toxoid.

There is no question but that tetanus toxoid is an active immunizing agent and that it would seem to be perfectly

possible to immunize individuals against tetanus. However, it remains to be seen to what extent it will receive practical application. The incidence of the disease in the general population is sufficiently low to make it questionable whether large-scale immunization would be advisable. There is no question but that such immunization should be of great value in that portion of the population whose occupations make them special tetanus risks, *i. e.*, agriculturists and men engaged in animal husbandry and military campaigns.

In actively immunized individuals, even though the immunizing injections were given a considerable time previously, and their serum antitoxin may be very low at the moment, it should be possible to protect them against tetanus by administering another dose of toxoid at the time of an injury. We have already spoken of the rapid and marked rise in serum antitoxin following a secondary stimulus. Thus, when a previously immunized individual is injured he is given an injection of tetanus toxoid instead of tetanus antitoxin. Such a procedure, of course, avoids the development of serum sensitivity in such an individual. There will then be a sufficient rise in his own antitoxin level within the incubation period of the disease to protect him against tetanus. Furthermore, it is possible, in soldiers and others running a particular tetanus risk, to keep their serum antitoxin at an effective level at all times by giving a single injection of toxoid every twelve to eighteen months after they first have been immunized.

It should be pointed out and emphasized that tetanus toxoid is of no value as a therapeutic agent. It should never be given during the course of the disease. It is solely an active immunizing agent and should be used only for prophylaxis against the possible development of tetanus following a future injury. Furthermore, because of the slowness of antitoxin development following a primary stimulus it should never be used as a prophylactic agent at the time of an injury in a person who was not actively immunized previously.

It is regrettable that there is no simple test, analogous to the Shick and Dick tests, to determine susceptibility to tetanus. An estimation of the degree of protection in an individual can be determined only by measuring the amount of antitoxin in his serum. This is an elaborate procedure which

would not be practical in any large group of individuals. Without such a measurement it is impossible to know if an individual is adequately protected. This difficulty may prove to be a stumbling block in the way of large-scale immunization against tetanus. Uncertainty cannot be tolerated when one is taking care of an individual with a serious injury that is likely to be infected with tetanus bacilli.

Since tetanus toxoid is simply a detoxified filtrate of a broth culture of the tetanus bacillus, it is very likely that unpleasant reactions may occasionally follow its use, particularly in adults. This has been the case with diphtheria toxoid. It is possible, of course, to develop methods of purification which may eliminate some of these reactions. Bergey<sup>30</sup> has already shown that washed, alum-precipitated tetanus toxoid is less likely to cause reactions than plain toxoid.

Ramon<sup>47</sup> has suggested the use of a "triple vaccine." That is, a mixture of tetanus toxoid, diphtheria toxoid, and typhoid and paratyphoid A and B vaccine is given in a single injection. These injections are repeated at two to three week intervals for three doses. Ramon has shown that the immunizing activity of each constituent of such a mixture is just as good as when given separately. We feel that this program might be applicable to newly mobilized troops. However, one would question its value for use in the general population, in this country, at least. Typhoid vaccination is not done as a routine procedure in practice, and, as we have already pointed out, it is questionable if wide-scale immunization against tetanus should be practiced.

#### MENINGOCOCCUS ANTITOXIN (FERRY)

Ferry and his associates<sup>50, 51, 52, 53, 54, 55</sup> have recently presented experimental data which they interpret as showing that the meningococcus produces a true soluble exotoxin against which a specific, neutralizing, antitoxin can be developed by the immunization of horses with this exotoxin.

The method employed for securing this exotoxin consists in cultivating the meningococcus in broth (Huntoon's hormone broth) for four to six days. The organisms grow in a heavy pellicle on the surface of the broth. After this period of incubation the broth is filtered through Berkefeld filters and

the resulting filtrate is said to contain an exotoxin. They have found that such filtrates contain a toxic substance specific for each of the four Gordon types of meningococcus and an additional toxic substance common to these four Gordon types.

These authors have shown that when their toxin is appropriately diluted in physiological salt solution it will, after its intracutaneous injection, cause a positive reaction, similar to the Dick reaction in a certain percentage of human beings. Individuals recovered from meningitis failed to give a positive skin reaction when injected intracutaneously with a toxin prepared from the same type of meningococcus as isolated from the patient. They claim that it was also possible to neutralize this reaction in susceptible individuals with the appropriate "antitoxin."

Ferry has immunized horses with his bouillon filtrates for the production of a meningococcus "antitoxin." The resulting serum has been used by him in a large number of animal protections and therapeutic experiments. Monkeys, rabbits and guinea pigs were used. Without reviewing in detail the numerous experimental protocols of this author, we may summarize by stating that Ferry has concluded from the data obtained that the meningococcus produces a soluble exotoxin and that a true antitoxin can be developed by immunization with this exotoxin.

In our opinion sufficient evidence has not been advanced to prove that the meningococcus produces a true, soluble exotoxin. It has long been known, of course, that the meningococcus produces a potent endotoxin. The reactions of this substance have been studied in great detail by Gordon<sup>56</sup> and by Murray.<sup>57</sup> Recently Malcolm and White<sup>58</sup> have published studies on meningococcus endotoxin. The reactions of animals to endotoxin, as described by Malcolm and White, are in no way different from those described by Ferry as being due to exotoxin.

The meningococcus is extremely susceptible to autolysis or self-digestion, which liberates intracellular toxic substances or endotoxin. This is particularly true when the organism is grown in a fluid medium. When the organism is grown in broth for four to six days there is abundant opportunity for the liberation of endotoxin by this autolytic process. There-

fore, immunization with such filtrates could result in the production of antiendotoxin. Such a serum need not be any different from the antibacterial sera produced by the usual methods of immunization with meningococci. We feel that Ferry's "antitoxin" is such a serum.

In Ferry's numerous protocols showing the protective and therapeutic effect of his "antitoxin" there is no evidence to show that it will neutralize in multiple proportions, which is a fundamental characteristic of true antitoxins. Furthermore, the effect of his serum, in the majority of instances, was studied in animals injected with living virulent meningococci, and there is no reason to believe that such effect was other than antibacterial. Furthermore, most laboratory animals, *i. e.*, rabbits and guinea pigs, are not truly susceptible to infection by the meningococcus.

An "antitoxin," moreover, could not be expected to rid the subarachnoid space of organisms, a result which is essential for cure of a patient with meningitis. No doubt such an antitoxin might relieve a patient of certain of his symptoms. On the other hand, there is no evidence that an antitoxin has any direct effect on bacterial cells. This has been abundantly demonstrated in the case of meningitis due to other organisms. For example, Dick antitoxin, regardless of the route of administration, does not alter the course of meningitis due to the scarlet fever variety of hemolytic streptococcus.

Hoyne<sup>59</sup> has recently published an analysis of a group of cases treated with Ferry's meningococcus "antitoxin." In this study 211 cases were treated with regular antimeningococcus serum and 85 cases were treated with "antitoxin." The mortality in the former group was 45.9 per cent, which is higher than that generally reported. The mortality in the antitoxin-treated group was 23.5 per cent, which is about the usual mortality rate given by others<sup>60, 61, 62, 63</sup> for patients treated with regular antimeningococcus serum. Furthermore, this paper loses much of its statistical value because, as the author states, in 40 cases the clinical diagnosis was not verified by smear or cultures.

Banks,<sup>64</sup> in England, has used meningococcus antitoxin in a small series of cases. The mortality in this group was 28 per cent. He concludes that this mortality is no better than



the standard mortality rate given by Flexner for patients treated with regular antimeningococcus serum.

In conclusion we are not trying to show that Ferry's "antitoxin" is without value. We have endeavored to point out that, in our opinion, it is not different from the usual antimeningococcus serum and there is no reason for using it in preference to such products. We do object to its being used on the assumption that it is a true meningococcus "antitoxin." The evidence is not sufficient to justify its being so considered.

#### STAPHYLOCOCCUS TOXIN, ANTITOXIN, AND TOXOID

Staphylococcus toxoid and antitoxin are of direct interest to the clinician as possible therapeutic agents in certain types of staphylococcus infections. Before they can be discussed, however, it is necessary to review the properties of staphylococcus toxin. Toxic properties of the filtrates of staphylococcus cultures were first observed in the early days of bacteriology. The modern development of the subject will be reviewed below. Acute interest in the entire staphylococcus problem was revived by the Bundaberg accident. In this unfortunate episode 21 children were inoculated with a diphtheria toxin-antitoxin mixture that was contaminated with staphylococcus aureus. Twelve of these children died of acute staphylococcus septicemia within twenty-four to forty-eight hours. However these children did not die of toxemia, but of an acute, fulminating staphylococcemia. This was shown by Burnet<sup>65</sup> and by the Report of the Royal Commission,<sup>66</sup> which investigated it. It was shown that the toxin-antitoxin was heavily contaminated with living staphylococcus aureus and that little, if any, soluble toxin was present in the mixture. Burnet<sup>65</sup> showed that the conditions under which diphtheria toxin-antitoxin mixtures were prepared and kept, even though contaminated by toxicogenic staphylococci, were unfavorable for the development of toxin. We mention this because a few recent students of the problem, in reviewing this occurrence, have implied that staphylococcus toxin was the important factor in the death of the children.

The toxic principles in filtrates of staphylococcus cultures manifest themselves, under experimental conditions, in several

ways. The important manifestations are as follows: (1) Hemolytic activity. Potent filtrates, even in high dilution, will hemolyze a suspension of erythrocytes. Rabbit cells are generally used for such purposes. (2) Dermonecrotic activity. Such filtrates, even when considerably diluted, will cause an area of erythema with marked central necrosis when injected intradermally into rabbits and other animals. (3) Lethal effect. Such filtrates kill animals with extreme rapidity when injected intravenously. Rabbits die within one to three minutes following the injection of an appropriate dose. Dolman<sup>67</sup> has found other animals, including the guinea pig, horse, cat, and mouse, to be susceptible and subject to this rapidly lethal effect. It should be pointed out that this is an unusual property for a bacterial poison. Practically all other bacterial toxins require a definite incubation period of at least several hours before their action is apparent. The lethal effect of staphylococcus filtrates appears to be due to a direct action on the A-V bundle in the heart. (4) Leukocidin effect. Potent staphylococcus filtrates have a destructive action on leukocytes. The older literature concerning these properties of staphylococcus filtrates has been reviewed by a number of recent investigators, including Burnet,<sup>65</sup> Dolman<sup>67</sup> and Weld and Gunther.<sup>68</sup>

That human beings are susceptible to the toxic principle in staphylococcus filtrates has been shown by a number of observations. In attempting to immunize patients with subcutaneous injections of small doses of toxin, Weiss<sup>69</sup> noticed that six to twelve hours after such injections there was often local redness and tenderness and occasionally swelling. He reported one instance where the injection of undiluted toxin was followed by intense inflammation and suppuration and with marked systemic symptoms. Pilot and Afremow<sup>70</sup> showed that the intradermal injection of diluted toxin in man caused a zone of erythema with swelling and tenderness within 24 hours. They were able to neutralize these reactions with immune horse and rabbit serum. Stevens<sup>71</sup> reported 3 cases of acute staphylococcus aureus infection with a scarlatiniform rash. It was difficult to distinguish the rash in these cases from that in scarlet fever. The rash could be blanched with staphylococcus antitoxin.

In discussing the properties of staphylococcus toxin, especially its effect on man, mention should be made of another substance produced by certain strains of staphylococci which causes an acute gastro-enteritis. This substance has been found responsible for a number of outbreaks of so-called "food poisoning." Such outbreaks have been described and others reviewed by Jordan<sup>72, 73, 74, 75</sup> and his associates. As has been shown by Dolman,<sup>76</sup> this "gastro-enteritis" principle is different from the toxin responsible for the effects enumerated above.

The production of potent staphylococcus toxin is dependent upon growing the organism under special cultural conditions as has been shown by Parker,<sup>77</sup> Dolman,<sup>67</sup> Burnet,<sup>65</sup> Parish and Clark,<sup>78</sup> Bigger,<sup>70</sup> Bigger, Boland and O'Meara<sup>50</sup> and Leonard and Holm.<sup>81</sup> In general, the most potent toxins are obtained by growing the organism in a semisolid agar with a buffered broth or peptone base. Cultivation is carried out under an increased carbon dioxide tension. The amount of carbon dioxide used has varied from 10 to 80 per cent in the hands of different investigators. The toxin is easily destroyed in an alkaline reaction which makes it imperative to use a buffered medium. It is possible that the effect of carbon dioxide may depend entirely upon its buffering action. After forty-eight hours' incubation the inoculated semisolid agar mass is squeezed through cheesecloth. The resulting fluid is centrifuged and filtered through a Berkefeld candle. The reaction of the filtrate is adjusted to slightly acid; pH 6.8. Staphylococcus toxin is thermolabile, being destroyed by heating to 60° C. for five minutes.

There is, apparently, no correlation between the invasiveness of a particular staphylococcus strain and its ability to produce a potent toxin. Stevens and Carp<sup>82</sup> studied 31 strains that were obtained from two sources. One group of strains was obtained from human lesions, such as furuncles, abscesses, and septicemias. The other group was obtained from the nasopharynx of normal individuals. The toxin produced by the various strains was apparently identical since the reaction of each toxin could be neutralized by the same antitoxic serum. There was no correlation between amounts and the properties of the toxins produced and the clinical origin of cultures.

With respect to the organisms isolated from acute infections there appeared to be no relationship between the severity of the infection and the ability of the corresponding strain to produce toxin.

There is considerable discussion in the literature as to whether the hemolytic, lethal, and dermonecrotic effects of staphylococcal filtrates are due to three different substances or whether these are different effects of a single toxic substance. On the basis of adsorption experiments Weld and Gunther<sup>65</sup> concluded that these different effects were due to different substances in the filtrates. On the other hand, nearly all other investigators subscribe to the view that a single toxin is responsible. Dolman<sup>67</sup> found that heating at 60° C. for different lengths of time caused the same relative effects on both the hemolytic and dermonecrotic titers. In studying the action of formalin on staphylococcus toxin Burnet<sup>63</sup> concluded that "all the characteristic activities of the toxin are lost concurrently in the process of formalin detoxication. In none of the experiments with partially detoxicated preparations has there appeared any indication that the three functions of the toxin, hemolytic, skin necrotic and lethal have been dissociated." Because there is practically complete agreement that the various manifestations of staphylococcus filtrates are due to a single toxin the Committee on Standards of the League of Nations<sup>64</sup> has provisionally adopted a method for standardizing staphylococcus antitoxin depending only on hemolytic activity. Separate assays dependent upon the dermonecrotic and lethal effects are not required.

All investigators are agreed that staphylococcus toxin is antigenic and that it is a true bacterial soluble exotoxin. The immunological reactions of this toxin and its antitoxin are, in general, the same as those which characterize true bacterial exotoxins as a class.

Staphylococcus toxin can be detoxified by formalin with great ease. After only a few hours' incubation in the presence of 0.3 per cent formaldehyde there is a marked reduction in its toxic action. After forty-eight hours' incubation it is practically completely atoxic. The toxoid is an effective immunizing agent.

Before reviewing the clinical use of staphylococcus toxoid

some consideration should be given to the question of natural antitoxin in man. This has been studied by a number of investigators, including Connor and McKie,<sup>85</sup> Ramon, Richon, and Descazeaux,<sup>86, 87</sup> Bryce and Burnet,<sup>88</sup> and Murray.<sup>90</sup> In general the presence of "natural" staphylococcus antitoxin in man is somewhat similar in its distribution to that of diphtheria antitoxin. According to Murray and to Bryce and Burnet, umbilical cord blood and the blood of newborn infants contains antitoxin in practically the same amounts as in the maternal blood. This is gradually lost during early infancy. In later years there is a gradual rise in antitoxin to what is assumed to be a "normal" level. Expressing his values in terms of International units Murray found an average value of 0.78 units per cc. for the blood of newborn infants; 50 cases having been examined. In 50 pregnant women he found an average value of 0.75 units per cc. This investigator also found that the level of antitoxin in patients with chronic pyodermias of various kinds was not significantly different from his "normal" value. In 7 patients with osteomyelitis, however, the average value was 11.7 units per cc. Parish, O'Meara and Clark<sup>89</sup> report similar experiences.

During the past few years a number of investigators, particularly Parish, O'Meara and Clark,<sup>89</sup> Murray,<sup>90</sup> Ramon, Bocage, Richon and Mercier,<sup>91</sup> Dolman<sup>92, 93</sup> and Connor and McKie<sup>94</sup> have treated patients suffering from chronic staphylococcal infections with staphylococcus toxoid. Patients are usually given a series of subcutaneous injections at weekly intervals. The initial dose is small, *i. e.*, 0.05 to 0.1 cc. and is gradually increased at each subsequent injection. A series has usually consisted of 4 to 6 injections. In many instances such a series of injections has been repeated one or more times. It has been found that in the majority of patients there has been a gradual rise in antitoxin level to many times the titer at the beginning of treatment. Murray has made the interesting observation that there appears to be an optimum level to which antitoxin will rise following the administration of toxoid. Further injections will not increase it. It is interesting to note that this level is quantitatively similar to that naturally present in patients with osteomyelitis. He suggests that measuring the antitoxic titer in patients'

sera provides a reliable index for stopping treatment. There is no purpose in administering additional toxoid when the level above referred to has been reached.

It is generally agreed that a majority of patients with chronic pyodermias such as recurrent furunculosis, pustular acne, recurrent stytes, blepharitis, carbunculosis and other superficial abscesses and sycosis barbae are considerably improved by treatment with toxoid. A small percentage of patients are not helped. Kindel and Costello<sup>55</sup> were unable to observe favorable results in their patients. Their work has been criticized by Dolman on the ground that they used a toxoid produced by a single strain of staphylococcus rather than a pooled toxoid from several strains. We cannot agree with Dolman in this criticism. There is no evidence at the present time that there is more than one antigenic type of dermonecrotic toxin. For this reason there is no justification for using a pooled rather than a monovalent toxoid.

In reading the several reports concerning the clinical value of toxoid it is difficult to form an independent judgment concerning it. In most reports the cases have not been presented in a sufficiently objective manner to permit the reader to judge for himself. Murray's report is an exception. From his tables and the manner in which he studied his cases, it seems apparent that many of his patients with chronic skin infections were definitely benefited. It should always be remembered, of course, that it is very difficult to control the appraisal of the effectiveness of a therapeutic procedure in this type of infection. One can never know which crop of furuncles would have been the last in a given patient even if no treatment had been used.

With regard to osteomyelitis there is no convincing evidence that toxoid is of value. In this connection we might recall again Murray's observation that the antitoxin level in such patients is essentially equal to the optimum amount occasioned by a series of injections of toxoid.

In summary, it is our opinion that staphylococcus toxoid is a useful agent in the treatment of chronic staphylococcal skin infections. For this purpose a toxoid of known antigenic potency should be used. Injections should be given subcutaneously, starting with a relatively small dose, *i. e.*, 0.05

or 0.1 cc. The dose can be increased gradually at subsequent injections. One of two series of 4 to 6 doses each may be given. Five to seven days should elapse between injections. If results are not obtained after such a course of treatment there is no point in continuing it further. If possible, it is a good plan to determine the antihemolytic titer of patients' sera before and after such treatment.

In our opinion there is no convincing evidence at the moment that staphylococcus toxoid is of any value in infections other than the group of chronic pyodermias. In the present state of our knowledge we cannot advise its use in osteomyelitis and generalized pyemic infections. Furthermore, it definitely should not be used in acute and fulminating staphylococcal infections.

Considerable work has been done with staphylococcus antitoxin during the past few years, both in experimental animals and in human infections. Parker and Banzhaf<sup>96</sup> were among the first to produce in horses a staphylococcus antitoxin which was capable of neutralizing the dermonecrotic effect of the toxin. We are not aware of any reports of the use of this serum in human infections.

Burnet<sup>65</sup> in carefully controlled experiments in rabbits was unable to obtain convincing results in experimental infections with living organisms. When antitoxin was given intravenously immediately after an intravenous injection of living culture, the life of the animals was prolonged. This author was also able to demonstrate the production of staphylococcus toxin in vivo. In three rabbits dying acutely from staphylococcus septicemia the pericardial exudate contained a skin-reacting substance that could be neutralized by antitoxin. On the other hand, when rabbits were actively immunized by the subcutaneous injection of living cultures they failed to die acutely, but invariably died in from four to thirteen days from generalized pyemic infections. Parish and Clark<sup>78</sup> and Parish, O'Meara and Clark<sup>89</sup> found that life could be prolonged in rabbits passively immunized with antitoxin.

These experiments have considerable significance. They indicate that antitoxin may protect against acute death in staphylococcus septicemia and suggest that such acute deaths may be due to the in vivo production of toxin. However, it

does not protect against late death due to widespread pyemic lesions. This is to be expected, since the antitoxin has no bactericidal action whatever. Nor can antitoxin be expected to protect against the development of widespread pyemic lesions during the course of acute septicemia. A similar situation exists in other infections. For example, there is accumulating evidence that septic complications are not prevented in scarlet fever patients passively immunized with Dick antitoxin.

Several reports have appeared in which staphylococcus antitoxin was used in human infections. Pantón, Valentine and Dix<sup>97</sup> report favorable results following its use in a small group of patients. Jamieson and Powell<sup>98</sup> are less enthusiastic in their use of antitoxin. While they do not give details of the patients in which antitoxin was used, they summarize their experiences as follows: "In staphylococcus pyogenic infections it has appeared that staphylococcus antinecrotizing serum has produced no uniformly good results. Vigorous intravenous and intramuscular antitoxin treatment in such cases extending over periods of from one or two to thirty days has sometimes had a favorable effect in reducing temperature and preventing daily chills, but blood cultures have in the main continued to be positive during serum treatment and metastatic infections have not been decreased or prevented. Local applications of staphylococcus antitoxin to abscesses have had a favorable effect in some cases; however, the efficacy of such treatment has not exceeded that commonly reported in the use of bacterial lysates." It is of interest to note the similarity of these results in human beings to those discussed above in experimental animals.

Dolman<sup>99</sup> has reported a large series of various types of staphylococcus infections and is an enthusiastic advocate of this form of therapy. However, because of the manner in which he reports his cases, it is difficult for the reader to form an independent appraisal of the results. At least his condensed mortality table is not convincing. Many of his cases received enormous doses of serum.

In summary, our own opinion, regarding the use of staphylococcus antitoxin is that it may relieve certain symptoms and may, in some cases of acute septicemia, prevent early death.



On the other hand, there is little reason to suppose it to have much curative value in subacute or chronic pyemia and osteomyelitis. Indeed, it might be said that antitoxin might change an acute, fulminating septicemia into the chronic type of pyemia with continuing positive blood cultures and developing pyemic abscesses. In the latter type of disease there is little to be expected from antitoxin treatment on the basis of existing evidence. It should be emphasized again that this antitoxin has no demonstrable bactericidal effect. We, therefore, feel that the therapeutic usefulness of staphylococcus antitoxin is limited.

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## CLINIC OF DR. JOE VINCENT MEIGS

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### RECENT ADVANCES IN MEDICAL GYNECOLOGY

THE purpose of this paper is to cover the recent advances in gynecology that are of value to medical men particularly. It is quite impossible to exclude certain advances that are of greater importance to surgeons and gynecologists. The subjects to be discussed cannot include all the advances but are selected by the author as necessary for the proper practice of medicine. Gynecology is so closely allied to medicine, endocrinology, physiology, pathology, and surgery that real gynecological knowledge should be all embracing. Under the last heading of this paper a short résumé concerning hormones, their commercial names, and a few explanatory diagrams will be found.

The present article is an attempt to classify the confusion of ideas as far as possible. It is clearly understood that many statements may prove to be incorrect later. If dogmatic statements are made they are made only to emphasize our knowledge as it is at the present time. Such a paper must be superficial and it is written only to aid practitioners who do not have the opportunity of working in research with the aid of well-equipped biological laboratories.

The subjects chosen to be discussed may be grouped under the headings—inflammation, tumors, pathologic physiology, and endocrinology. The necessity of giving credit where due in such a paper is not feasible and the author hopes that the lack of references to men responsible for outstanding pieces of work will be understood both by them and by their readers.

### NEW DIAGNOSTIC METHODS

First to be considered should be advances in the methods of diagnosis. It is now clearly established that certain urine and blood tests for the presence or absence of pituitary or

ovarian hormones are of great value. Estrin<sup>1</sup> is present in the normal patient's urine and anterior pituitary prolan<sup>2</sup> is not. In the blood of the normal patient estrin can be detected and occasionally anterior pituitary prolan. In ovarian failure estrin should be absent and pituitary prolan present in both blood and urine, while in pituitary failure neither should be present in either. Blood tests are difficult to do but the urine tests are perfectly satisfactory so that the findings in the twenty-four hour specimen of urine and the morning specimen of urine are sufficient. Just before the menstrual flow the estrin content drops markedly and this fact should be taken into consideration when studies are made. Following removal of the uterus, if both ovaries are retained, the findings are just as in normal women. Removal of the uterus does not cause an early menopause if the ovaries are healthy and are left with an intact and satisfactory blood supply. The table below showing urinary findings has been used with considerable satisfaction in our Ovarian Dysfunction Clinic. Its absolute accuracy may be questioned, but as a working table its value is great.

	<i>Estrin.</i>	<i>Pituitary prolan.</i>
Normal.....	+	0
Ovarian deficiency.....	0	+
Pituitary deficiency.....	0	0
Pregnancy.....	+	+(pregnancy urine prolan)

After the test of a patient's urine has been reported, and more than one test should be made, the probable factor in the patient's difficulty should be manifest. For instance a patient with no estrin and positive prolan would be considered to have an ovarian deficiency.

Another valuable method of diagnosis is endometrial biopsy. This can be carried out in the office either with or

<sup>1</sup> As used by the author the term estrin includes all chemical types of estrogenic hormones.

<sup>2</sup> Anterior pituitary prolan is that substance from the anterior pituitary gland that brings about follicle formation, ovulation, and luteinization in the experimental animal ovary. It is recovered from the pituitary itself. Pregnancy urine prolan, or the so-called "anterior pituitary luteinizing hormone," is present in the urine of pregnant women and is that hormone that is responsible for the Aschheim-Zondek test and Friedman test. It has been on the market for some time under the various commercial names described in the section on hormones.

without a short anesthesia. The following methods are in vogue at the present time; the punch method, the suction curette method, and the small cup curette method. By means of the punch and small curette a piece of tissue can be removed from a given place in the endometrium while the suction curette removes much more tissue but the area from which it was removed is not so definite. If, as has recently been reported, we are to find different types of epithelium in different areas of endometrium perhaps the suction method is best, as it removes more than one piece. The value of the biopsy lies in the fact that the pathologist should be able to tell whether or not a given patient has ovulated. The so-called "premenstrual, progestational, or secretory phase" does not occur without ovulation. Therefore if a specimen is removed about the twentieth to twenty-fifth day after onset of a menstrual period secretion should be present, if it does not show secretion the patient may not be ovulating and therefore her flow comes from a proliferative or estrin phase and not from the corpus luteum or secretory phase. This fact might account for her menstrual abnormality or sterility. This simple test has been of immense value in determining late ovulation, early ovulation and anovulation and gives accurate evidence of the results of hormone treatment.

The measurement of the uterus is an important aid in investigation of the gynecologic patient. This is done with an instrument devised by Samuel Meaker and consists of an ordinary uterine probe marked in centimeters and a collar that can be moved up and down the shaft to allow readings of the length of the cervix from the external to the internal os and the length of the uterine canal from the external os to the top of the fundus. The normal measurements of the whole uterus to the cervix should be in the proportion of three to one; in the juvenile uterus it is as two to one, and in the infantile with its long conical cervix as one to three. These measurements are easy to obtain and may be the clue to the reasons for amenorrhea, dysmenorrhea, sterility, etc.

Congenital erosion of the cervix has been observed in both anatomical and function disturbances of the genital tract. The name is not a true descriptive term for the condition is not a true erosion but a maldevelopment of the cervix. The circular



strawberry-red area surrounding the external os of the virgin cervix is made up of endocervical glands and is a stigma of hypoplasia. The uterus is not normally developed if the endocervical glandular epithelium is not properly drawn up into the cervical canal. The "erosion" is the exposed endocervical epithelium. Unquestionably this type of cervix tells a story of underdevelopment and many instances have been seen in our clinic that prove the importance of the consideration of this lesion in proving hypoplasia. It is a stigma of lack of normal development and should be carefully watched for.

Molimina or premenstrual feelings, probably due to increasing estrin production, are of importance. The normal woman can usually tell when her next period is due by the "feelings" of depression, easy weeping, backache, bloating, bearing-down, painful breasts, pimples, cramps, and whitish discharge. Many other sensations are noticed but the above are the most common. If a patient with amenorrhea has such rhythmic feelings it is certainly a sign of ovarian function for with the ovaries removed these feelings vanish. With the ovaries present and the uterus out molimina are still present. Such "feelings" may give a clue to the proper time to start treatment in the amenorrheic patient and the dates of such occurrences are of considerable worth. A lack of molimina in the amenorrheic patient may indicate a primary ovarian dysfunction and in a patient such information would be of enormous value.

Hirsutism, or abnormal growth of hair, is a common finding in our clinic and is difficult to evaluate. Without doubt certain women have more masculine characteristics in their make-up than others, just as certain men have more femininity than others. Also certain races tend to moustaches and beards and hairy arms, while others do not. If the hirsutism has been present since youth its significance is not so great as when it suddenly appears. The recent onset of hirsutism in a woman may mean nothing serious or it may mean the onset of a masculinizing process due to pituitary disease (basophilism), adrenal cortex disease, or a masculinizing tumor of the ovary (arrhenoblastoma). Certainly such evidence is of importance.

In another field altogether are two investigative methods that are proving of more and more importance. Most of us

cannot interpret the findings correctly as yet but practice will prevent serious lesions from developing under our observation. Cancer of the cervix, next to cancer of the breast, is the most common lesion of malignant neoplastic nature that woman has. If earlier diagnosis is possible then we must all familiarize ourselves with the method. Schiller found that iodine in the form of Lugol's solution, if applied to the normal healthy cervix, stained it a dark brown. He found that it stained scars, erosions of the cervix, and chronic inflammatory processes a lighter shade of brown but he also found that Lugol's solution did not stain leukoplakia or early cancer of the cervix at all. This lack of staining is due to lack of normal glycogen content of the cervical epithelium. Therefore, with a vaginal speculum and a nasal spray full of Lugol's solution, with the cervix gently wiped dry with cotton, a very important observation can be made by any one. If on such an examination a white patch of any size is discovered the patient should be investigated further. The piece of tissue should be examined microscopically to determine the type of lesion, and if leukoplakia the offending area or cervix should be removed, and if cancer the uterus should be removed or radium applied, depending upon the advice of the surgeon or gynecologist. Hinselmann has developed the colposcope (vagina scope) to a high degree of usefulness and his writings and the writings of others clearly describe the appearance of leukoplakia, premalignant or malignant conditions of the cervix. This instrument magnifies the cervical epithelium ten times and makes the observation of small areas of atypical epithelium easy. Without doubt small areas may be seen that cannot be detected with the naked eye and large areas of abnormal tissue may be studied more carefully. Mucous secretory ducts, Nabothian cysts, irregularities in the smooth epithelium, and leukoplakia are easy to detect. Not all can own such an instrument, but there is no doubt about its value and its usefulness.

#### INFLAMMATION

Advance has been made in the interpretation of vaginal discharges. The most important is the recognition of the *Trichomonas*. This flagellate is frequently found in women

without symptoms but more often it is the cause of an irritating, odorous, profuse, white to yellow discharge. The patients frequently complain of a disagreeable feeling and irritation of the vulva and inside of the legs. Recognition is easy. A drop of discharge is placed on a glass slide with a drop or two of warm water added and covered with a cover slip. The high dry power of the microscope is used. The light is cut well down and structures the size and shape of pus cells can easily be seen jerking their way in the moist smear. They may be confused with phagocytic cells, but if watched carefully small whips can be seen at the periphery of the cell. The complete configuration of the trichomonas is rarely seen. These organisms are most often part of a mixed infection so that pus and bacteria are commonly present.

The treatment is not easy. Many cases are encountered but few cured. The variety of the methods of treatment show that there is no specific one. It is very important to instruct the patient to wash the vulva and perineum carefully after each defecation; she must also be instructed to wipe the anus from front to back and not back to front. In the office the vagina should be gently cleaned out with dry cotton or cotton soaked in green soap and water. Then the treatment can be applied. The vagina may be painted with pure pyroligneous acid and soft tampons covered with Lassar's paste inserted to balloon out the vagina. The tampons are removed in forty-eight hours and douches of one teaspoonful of a 1: 100 solution oxycyanide of mercury to one quart of water are used daily. Another treatment after cleaning of the vagina is to use picric acid vaginal suppositories 1 grain each night, washing out the suppository each morning with a douche of sodium perborate, one teaspoonful to one quart of warm water. The patient should be warned to wear her menstrual gear at night, as the picric acid stains the night clothes. Stovarsal powder in a powder blower used two to three times a week in the office frequently clears the condition. Recently Devegan tablets (Winthrop Co.) have proved effective. Two tablets are placed high in the vagina at night and are douched out in the morning with one teaspoonful of sodium perborate in one quart of warm water. The treatment continues till tablets and douches are no longer necessary.

All of the above treatments make the patient comfortable, but do not guarantee that the infection will not return if the treatment is neglected or given up. Cures sometimes seem easy but recurrences are easier. There is no one method of absolute cure.

Monilia infections are of a similar sort and cause a vaginitis with a more watery discharge occasionally with white pieces of tissue in it. The diagnosis is made by staining some discharge on a slide with Gram's stain and looking for yeasts and long branching mycelia. The treatment is cleanliness, careful wiping of the vagina and the use of alkaline solutions, such as mild sodium bicarbonate douches, and glycerin and borated sodium bicarbonate suppositories. The use of 1 per cent aqueous solution of gentian violet painted over the vagina is of considerable value.

Much has been written of the treatment of vulvovaginitis of gonorrheal origin in children. This infection is very persistent and resistant but the knowledge of the ability of estrin to change the infantile vaginal mucosa to adult squamous epithelium is the basis of a new treatment. Five hundred international units of estrin by mouth daily will suffice to change the epithelium. When the epithelium becomes adult in type the gonococcus is supposed to remain no longer as an inhabitant of the vagina. There is no doubt that this form of treatment will change the lining of the vagina. Although relief of symptoms is early and easy and the vaginal changes can be watched by vaginal smears under the microscope, nevertheless the cure of this condition by this method is not always accomplished. Certainly it is a step forward and no untoward reactions have been seen in the children. Occasionally, if the dose is too large, the patient will complain of swelling in the breasts, and in one case a moderate amount of vaginal bleeding ensued.

The treatment of pruritus vulvae is still difficult. Absolute cleanliness, the use of carbolic acid lotions and other mild analgesics are helpful, but if the pruritus is persistent and the discomfort of the patient extreme, alcohol injection under an anesthetic may be tried. If one to 2 drops of 95 per cent alcohol are injected  $\frac{1}{4}$  to  $\frac{1}{2}$  inch apart at the periphery of the area of pruritus relief can be obtained in some of these

very difficult cases. The vulva may swell after the treatment and remain painful for a few days. Not over 10–20 cc. of this solution should be used at one time.

It should not be forgotten that diabetics frequently have itching of the vulva and a urine analysis must always be done. Many cases of pruritus are due to epidermophytosis and eradication of this infection is frequently followed by relief. The use of mild salicylic acid and benzoic acid preparations, the strength depending upon the amount of cracking and fissuring of the skin, is advocated. Cleanliness, and avoidance of scratching are important factors in the cure.

The severe itching and discomfort of leukoplakic vulvitis and kraurosis vulvae are best handled by radical excision of the vulva. Both lesions are precancerous and radical surgery cannot be criticized. Section of nerves crossing the perineum is advocated but often falls far short of cure and if operation is to be done vulvectomy with removal of diseased tissue is probably safest.

### TUMORS

Tumors of endocrine significance are not uncommon but recognition of them has only been recent. Certain of these tumors are accompanied by subnormal development of the host, others cause masculinization and still others, femininization. The knowledge of the existence of such tumors is important and if a patient with certain peculiar characteristics has an unusual tumor the cause and effect may be evident. The ovariotesis or combination testicle and ovary is rare, and is often accompanied by hypospadias. The testicular tubular adenoma of Pick is a type of arrhenoblastoma (arrhenos meaning male) and may cause mild masculinization and failure of the ovaries and removal allows femininity to redevelop. The suprarenal hypernephroma either of the suprarenal gland itself or of the ovary causes a severe masculinization. In cases of masculinization of recent development such lesions must be looked for. In basophilic adenoma of the pituitary (Cushing's syndrome) amenorrhea and masculinization with marked hirsutism are not uncommon. The disgerminoma or seminoma of the ovary may be accompanied by a neutral development of the patient, the sex organs being rudimentary or with only partial develop-

ment. Femininizing tumors are of the granulosal, lutein or thecal types and are accompanied by the secretion of estrin and by menorrhagia before the menopause and abnormal bleeding and resumption of periods after the menopause. The granulosal cell tumor is more frequently malignant than benign. Its removal with removal of its estrin secretion allows the patient to return to normal. The luteoma, a rare tumor, is probably a granulosal cell tumor that has changed, as it physiologically could, into a tumor of luteinized granulosal cells. The existence of luteoma is often questioned. These various neoplasms must be borne in mind for neglect or ignorance of them might result in a disaster for their malignancy, excepting the first two, cannot be underestimated.

### OVULATION

Much work has been done in attempts to establish the time of ovulation. If ovulation time were accurately known the treatment of sterility would be aided and the prevention of conception made easier. The ovum is supposed to live but twenty-four hours and the spermatozoön for three days, therefore if the time of ovulation were accurately established this time could be avoided for four days as a method of contraception or be used to aid in conception. The consensus of opinion seems to be that ovulation takes place from the twelfth to the seventeenth day after the onset of the menstrual period. Therefore from the ninth to eighteenth days after the onset of the catamenia is either the time to avoid or to indulge in intercourse, depending upon the result desired. Some patients can easily determine the exact time of their ovulation for they notice a sensation of gas or discomfort in the abdomen at the midmenstrual point. This happening is probably due to ovulation and if the pain or symptoms are exaggerated the patient is frequently operated upon for appendicitis and a normal appendix removed. Careful inspection of the ovaries at the operation would disclose the fact that a follicle had just ruptured and coagulum and blood would be found in the pelvis. Certain other patients notice a regularly occurring midmenstrual flow or pink discharge which is due to bleeding probably by diapedesis from an endometrium congested at the time of ovulation. Because of the drop in estrin that

occurs at this time bleeding occurs. Careful questioning of the patient regarding every possible factor in the menstrual cycle often proves of great value.

Operations in young girls for chronic appendicitis are often due to ignorance of the physiology of the ovary. Lack of a proper exploration of the patient's pelvis fails to reveal the true reason for the pain. Girls with mild pain at the intermenstrual point can be carefully watched and if no untoward symptoms develop surgery can be avoided. This at least is an important outcome of our more enlightened knowledge of normal ovarian physiology.

#### SEX DETERMINATION

Although many have searched for a means of determining the sex of the unborn child no discovery of importance has as yet been verified. Certain suggestive findings have been reported but none that has proved satisfactory. Studies of the blood and urine to determine the presence or absence of estrin to prove the sex in cases of hermaphroditism and patients without vaginas have no value. It is not possible to establish the proper sex by hormone determination.

#### FRIGIDITY

To relieve frigidity in the female has frequently been the goal of medical men and gynecologists. The problem has not been satisfactorily answered as yet but certain investigators while giving patients huge (100,000 to 200,000 I. U.) doses of estrin to bring about menstruation in the amenorrheic have noted increase in libido during treatment. This opens a field for speculation and the use of estrin may prove of value in some cases. It is just as sure, however, that in other cases it will be of no value whatsoever. Smaller doses may be tried for the expense of huge doses of this hormone is too great for most to bear. The reaction of patients after the menopause is of interest—some patients are completely frigid, some have a greater libido, and some are unchanged. Perhaps it is lack of estrin that determines the problem, but there is no definite proof as yet, although estrin has aided frigidity in certain cases. Some patients after x-ray treatment given to destroy the ovaries, note an increase in libido for a short time and after

a few months a great loss of feeling. Unquestionably all patients who are to have x-ray treatment over the pelvis should be warned of the possibility.

Careful and thoughtful psychological examination is the most useful method of investigation and sympathetic history taking may unravel an unexpected situation. Certainly dyspareunia or painful coitis makes for frigidity and if this can be cleared up frigidity may vanish.

### STERILITY

The study of sterility and fertility is fascinating and the number of investigators enormous. There are certain facts that seem important and are rather new. The anovulatory cycle is of paramount importance—though suspected as a possibility for years, only lately has the fact been established. Many women flow irregularly and a few absolutely regularly without having a graafian follicle rupture. Of course if ovulation does not occur no woman can conceive. To establish the presence of ovulation it is necessary to curette the endometrium or do an endometrial biopsy. This should be done on about the twenty-fifth day after the onset of menstruation. If such a piece of tissue shows only a proliferative or estrin phase and no premenstrual or secretory phase and the patient flows shortly afterward she can be considered as going through an anovulatory cycle. There is no absolute cure for such a condition and before any treatment is instituted the test should be repeated, for it has frequently been noted that after such a curettage or biopsy the patient has become pregnant. It has also been noted that after an endometrial biopsy the next biopsy shows a premenstrual or secretory phase. These facts probably explain the frequent occurrence of pregnancy following dilatation and curettage, following the Rubin test, and following lipiodol injection of the uterus to determine the patency of the tubes. Trauma of the cervix or the uterus may be the responsible factor (just as in the rabbit, ovulation does not occur without copulation). Trauma followed by ovulation, no period and conception—this sequence of events has occurred so frequently that the probability is perhaps a fact. Another method of inducing ovulation is to use one of the anterior pituitary sex hormones (not



pregnancy urine prolan, the anterior pituitary-like hormone) in an endeavor to stimulate follicle formation. It is not certain that it always occurs and that if it does that ovulation takes place, but it should be a more satisfactory method of treatment than the use of prolan from the urine of pregnant women. The use of pregnancy urine prolan in sterility work is fraught with danger, for many investigators feel that this substance causes changes in the ovary suggestive of atresia, the opposite effect to the desired one. Estrin, as it does nothing to the ovary and as it is supposed to inhibit the action of the pituitary, should not be used. Yet certain men interested in sterility work have no hesitancy in reporting its success occasionally, but the explanation is not known.

Certainly in sterility cases the measurement of the uterus is important. Many a uterus that feels large on examination is really infantile or juvenile in structure and although a patient with this type of uterus may become pregnant, nevertheless in a sterility case knowledge of the hypoplasia is of great importance.

Thyroid is an important agent in treating sterility patients and many have conceived after taking small amounts ( $\frac{1}{2}$  grain daily) for short periods of time. In patients with low metabolisms this is of great importance, but even in those patients with normal metabolisms treatment with thyroid has proved of value.

A factor frequently overlooked but of great significance is the condition of the ovum or spermatazoön. The so-called "blighted" ovum is due to a defective ovum or sperm and it is very possible that defective germs are produced because of an intrinsic fault in a patient's gonads. The production of such a defective ovum may allow menstruation in all its phases to take place but completed pregnancy may never occur.

Habitual abortion is not actually a problem of sterility, yet the patient who aborts is sterile as far as a living child is concerned. The problem here is perhaps overactivity of the estrin-primed uterus due to lack of the quieting corpus luteum hormone, progesterin. The first endeavor to treat this condition was the attempt to create an effective corpus luteum in the ovary by using pregnancy urine prolan to stimulate luteinization. Now that we suspect that this hormone (preg-

nancy urine prolan) does not cause luteinization it is not wise to use it. Progesterin is now on the market under the trade names of Corlutin and Proluton. This substance, if potent, should be able to quiet the estrin-irritated uterus and in some cases it has done so, preventing habitual abortion and allowing pregnancy to proceed to its conclusion. The dosage should be  $\frac{1}{10}$  to 1 rabbit unit two to three times per week.

Apparently vitamin E is important in patients who abort habitually. It has been shown that lack of vitamin E causes death in utero. This vitamin is easily available in lettuce and in wheat germ oil. The latter is now on the market and 5 to 10 drops daily is a sufficient dose.

### THE BREAST

The breast is acted upon by estrin and progesterin. Estrin acts upon the duct system and progesterin upon the alveoli. After the breast has been properly primed by these two hormones during pregnancy prolactin (from the anterior pituitary) acts upon it and causes lactation. Lactation has not been produced in castrated women by this method but marked and suggestive changes have occurred in the breast.

The premenstrual painful breast may be due to overstimulation by estrin. To relieve the pain and discomfort it is necessary to diminish such secretion. One method would be x-ray treatment of the ovaries or destruction of the pituitary secretion that stimulates the ovaries. Obviously these are not the proper methods, therefore, inasmuch as we believe excess of estrin will inhibit the pituitary gland estrin should be used before the oncoming period and omitted about five days before it is due. Thus the pituitary would cease secreting and in the remaining five days before the oncoming period would not have time enough to produce more estrin from the ovary. Therefore the estrin content would be reduced and consequently less pain occur in the breast. This theory is not without its defects but surprisingly enough the treatment is effective in many cases. Six hundred international units of estrin given daily except for the five days before the oncoming period has proved effective.

Another condition in which to use our knowledge of breast physiology is in the breast that lactates after cessation of

nursing or the breast that lactates and swells at the time of weaning. Prolactin (an anterior pituitary hormone) will not act in the presence of estrin, therefore large doses of estrin should stop lactation. It has been found that if live pieces of chorion are left in the uterus after delivery lactation is prevented. This is because the chorionic tissue secretes estrin, which prevents the action of prolactin.

It is conceivable that chronic cystic mastitis, a disease more frequent in the unmarried woman with unused breasts, may be due to constant stimulation of the duct epithelium by estrin with no letup of this stimulation such as occurs in pregnancy and lactation.

Treatment of the bleeding nipple by means of estrin has been advocated by Mazer, who believes that excessive anterior pituitary lobe hormone causes an abnormal response of the alveolar system. He believes that this type of mazoplasia may be accompanied by papillary growth in the upper ducts and is due to lack of estrin as well as increase of anterior pituitary hormone. The treatment should be inhibition of the pituitary by more estrin and he has found that this treatment is satisfactory to check pain and stop bleeding. That there is danger in such a method of treatment is unquestionable, for bleeding from the nipple may be due to a papilloma and this papilloma may be a serious one and not a benign one. Also certain cancers of the breast are accompanied by bleeding and differentiation between the two is difficult.

One of the most satisfactory forms of treatment of breast discomfort is the use of a proper supporting, as contrasted to pressure, brassiere. This simple expedient is frequently overlooked and its importance cannot be overestimated.

#### PREGNANCY TESTS

The Aschheim-Zondek and Friedman tests are from 90-98 per cent perfect. Most of the failures have a real explanation and some negative results are proven positive upon a repeat test. It is not wise to conclude that a patient is not pregnant if signs point toward pregnancy till at least two tests have been completed. False positives are often due to different types of female sex dysfunctions.

The use of pregnancy tests to diagnose extra-uterine preg-

nancy has not met with universal agreement. The Friedman or rabbit test should be used because of its quickness. If an extra-uterine pregnancy is suspected and the patient is in excellent condition and not bleeding, the test should be done. but if the patient is ill and there is an abdominal emergency. operation is the proper treatment and an attempt at too fine a diagnosis might prove disastrous. The test should be positive as long as any living chorion is present in the tube or abdomen.

The Aschheim-Zondek or Friedman test should be negative seven days after termination of pregnancy. The presence of living chorionic tissue will continue to give a positive reaction. If such a reaction persists the question of retained products or of chorionepithelioma should be raised. High titers of ten to fifty times the usual amount of prolan should be considered as a serious finding. In hydatid mole the test is high and in chorionepithelioma very high. If after a mole, chorionepithelioma, or pregnancy, a test that has been negative becomes positive a very serious condition has probably arisen, either tumor has developed or recurred or a metastasis taken place. If the test persists after miscarriage, pregnancy, or mole a curettage should be done and if it is positive after this a diagnosis of possible tumor must be made and hysterectomy is justified. If the test persists after the hysterectomy then it is probable that a metastasis has taken place.

Certain teratomas of the ovary containing chorionepithelioma give positive tests, and the finding of a tumor in the pelvis not a pregnancy with a positive test should make one suspicious of this type of lesion.

#### AMENORRHEA AND DELAYED MENSTRUATION

Amenorrhea is an expression of absent ovarian function. If primary, its cause lies in the ovary itself, and if secondary, in some outside influence that affects the ovary. In the treatment of such a condition it is necessary to know the type of amenorrhea the patient suffers. A study of the hormones present in the urine helps. If estrin is absent from the urine and prolan is present, the ovary is primarily at fault. If, however, prolan (from the pituitary) is also absent the ovary may be able to function but stimulation of it is absent. Endometrial biopsy will also indicate whether the ovary is

going through any sort of cycle or whether it has ceased to function. There is no doubt but that influences other than the pituitary may be at work. For instance, in hyperthyroid states or myxedema, the ovary often ceases to function. Any debilitating disease such as tuberculosis, allows the functions least necessary to life to cease. As the reproductive function is the least necessary for carrying on life, it is early affected in disease. Once the reason for the amenorrhea is established intelligent treatment can be carried out. If the cause is prolonged illness it can be treated with hope of cure. If pituitary dysfunction is responsible, then the hormone of the anterior pituitary should be tried. Doses of Prephysin (Chappel) from 25 to 200 units should stimulate the follicles of the perfectly good ovary and ovulation may follow. The use of this extract has certain dangers as overstimulation of all follicles might result. It is conceivable that too many of the follicles might be stimulated and this might have serious consequences. If the ovary itself is at fault the stimulation with pituitary hormone is again advised though the result may be unsuccessful, for if the ovary is too far atrophied then no stimulation will revive it. Such treatment is, however, perfectly justifiable.

Estrin and progestin can be used to bring about a menstrual period but as ovulation does not occur in such instances its value can only be psychic and the expense of the large doses necessary (100,000 to 200,000 international units of estrin and 10 to 50 rabbit units of progestin) are prohibitive. It is possible that such a treatment by bringing about a menstrual cycle might cause it to continue, but there is no reason for expecting such a result.

It has frequently been noted that patients with thyroid underfunctions are amenorrheic and the wise use of this extract has proved of value in many instances. Thyroid is of real value in amenorrhea and should always be tried, but the basal metabolism should be used in conjunction with it.

Estrin itself may cause the endometrium to develop and proliferate and when withdrawn may allow bleeding to occur. This bleeding is bleeding from the proliferative type of endometrium only as no secretory change can be brought about by estrin alone. Ovulation has not occurred. Psychologically

this bleeding may be of value to the patient but it is not a physiologically perfect result.

The amenorrhea of obesity and certain functional disturbances as well as those due to wasting disease are the ones most likely to respond to treatment. Real deficiencies such as pituitary or ovarian are much less likely to respond.

There are types of temporary amenorrhea associated with follicular cysts of the ovary that can be treated either by means of surgery (excision or puncture of the cyst) or even rupture of the cyst by bimanual examination, though this latter type of treatment is not recommended.

The use of estrin to develop a small uterus, especially when the uterus is considered the organ at fault, has its advocates and if large doses (1000 to 3000 I. U. of estrin) are used daily over monthly intervals, it is conceivable that such an effect could be brought about.

Amenorrhea should not be allowed to continue untreated in girls of child-bearing age, because if the delay in the catamenia is allowed to progress beyond a year, cure of the condition is very unlikely. Prompt treatment of the undernourished, sick, and underdeveloped, and the use of thyroid and pituitary hormones should be instituted early in the dysfunction if results are to be obtained. The same treatment should be accorded those individuals who have a delayed onset of periods (menarche) and great industry should be employed to bring about the onset of flow. If a girl has not had a period at the age of sixteen then treatment should be undertaken. Proper hygiene, endometrial biopsy, anterior pituitary prolan, thyroid, etc., should be employed early.

Certain anemias of youth are often accompanied by amenorrhea and such blood dyscrasias should be investigated and the anemia corrected. A secondary anemia of the chlorotic type may be responsible and the response of the dysfunction following treatment of the anemia with iron is often striking.

Cysts of the corpus luteum with a persistent secretory phase and decidual formation in the endometrium are possible and although cases have been reported in the literature they are not common. Such pathology should, however, be searched for and if found, the cyst should be excised.

## DYSMENORRHEA

The study of dysmenorrhea is far from finished and the problem is so great that only the barest outline of procedure and treatment can be outlined. Dysmenorrhea occasionally responds to psychotherapy, to medical treatment, to hormone therapy, and to surgery. Many are the tools of the profession in the treatment of the condition but few the complete cures.

Pelvic examination in patients with dysmenorrhea may disclose a small, underdeveloped, anteflexed or retroflexed uterus, or a small-sized uterus in normal position or retroversion, or a large boggy uterus in retroversion, or even a normal-sized uterus in good position. Pelvic inflammations, intramural or submucous fibroids may also be possible causes and must be borne in mind.

The typical uterus of the patient with dysmenorrhea is either ante or retroflexed and is usually of smaller rather than larger development. Measurement of the uterus if the hymen is ruptured, may give a clue to the proper treatment, for if it is underdeveloped attempts at further development should be carried out.

That psychic disturbances are causal factors cannot be denied but often after careful investigation with mental relief to the patient dysmenorrhea continues. Without doubt dysmenorrhea may be made much worse by an over-solicitous mother and over anxiety at the time of the catamenia is an undoubted factor. However, such patients may have dysmenorrhea after marriage when away from maternal solicitude and not be relieved till after the birth of a child. There is a goodly percentage of cases in which dysmenorrhea recurs after childbirth, to the consternation of the doctor, who said that childbirth would cure it. There is no absolute cure except hysterectomy and this should not be considered until the very last resort.

The first treatment should be carried out by the family doctor, who should try to correct any worries that the patient may have and he should warn the anxious parent against pitying the child too much. The health of the patient should be noted and any sign of underdevelopment or undernourishment corrected as far as possible. If the uterus, on rectal

examination, is found to be flexed forward or back and of small size, then the use of estrin is indicated. Whether or not growth actually occurs is not altogether settled but it is theoretically sound and worth trying.

The inhibiting action of estrin is another reason for its use and certain cases are much relieved by giving subcutaneously 50,000 I. U. seven days before the onset of the coming period in one dose. Estrin, when used in this fashion, is supposed to inhibit the pituitary gland from secreting prolactin A that in turn causes secretion of estrin in the ovary. If we believe that estrin sensitizes the uterine musculature, which it probably does, then we can lower the amount of estrin present at the time of menstruation by the above method. By giving a large dose before the oncoming flow we prevent the pituitary from causing the ovary to secrete more estrin and in the seven days left before the period is due there will not be time to manufacture more and the estrin given subcutaneously will have been used up. Thus at the time of onset of the catamenia the estrin content should be low and the uterus not as sensitive. This method has been successful many times and its use is advocated. The reasoning for its use may not be correct but the results obtained justify the therapy.

It is known that the hormone of the corpus luteum, progesterone, causes a cessation of motion in the uterine musculature brought about by estrin. It would seem logical, therefore, to use progesterone to quiet the sensitized uterine musculature and thus cause a cessation of cramps. This should be a valuable method of treatment now that progesterone is available for use. The dosage should be as large as the individual patient can afford and from 1 to 50 rabbit units could not be too great a dose.

The above method has been tried before but in a different way. Pregnancy urine prolactin was supposed to cause luteinization and thus bring about a secretion of progesterone *but* until it is more definitely settled that pregnancy urine prolactin does affect the ovary and how it does its use is theoretical only. The consensus of opinion now seems to be that pregnancy urine prolactin produces atresia in the ovary and that although theca luteinization may occur real luteinization does not. That these observations are correct is another question and only



further study will prove them. Certainly the effects of pregnancy urine prolan on the ovaries of mice and the presence of lutein cysts of the ovary in hydatid mole and chorionepithelioma (when the urine contains immense quantities of pregnancy urine prolan) makes it difficult to doubt the luteinizing power of pregnancy urine prolan.

When the above methods of treatment have been tried and have failed the use of dilation in the office with small dilators is advised. It has been noted that after a uterus has been measured with Meaker's hysterometer in a patient with dysmenorrhea that the next period may be less painful, and recently it has been suggested that small-sized uterine dilators be passed through the internal os as an office treatment for the same reason. This method of treatment, if done with surgical asepsis, should prove of great value. Dilation, as carried on this way, may be too little and the patient should then be subjected to proper dilation under an anesthetic. This stretching should be thorough and carried out for at least fifteen minutes. At the same time, while the patient is under an anesthetic, it should be noted if there is a tight band about the internal os. This band, similar to the hard band-like tissue found about a pyloric stenosis in infants, can be easily felt on rectal examination. It is not difficult by placing a knife in the cervical canal as far up the internal os and with a finger in the rectum to make an incision directly posterior and cut across the hard band. A small piece of gauze is then placed in the incision to keep the constricting band open and from healing in its original position.

If all treatment has failed so far the patient should have an abdominal operation and a suspension of a flexed or retroverted uterus. At this time a resection of the presacral nerve or superior hypogastric ganglion should be carried out, for this method of treatment has given the highest percentage of complete cures of any procedure except hysterectomy. There are failures even from this operation and the failures are probably due to anomalies of these nerves and lack of section of them. This cannot be avoided and although results are good in nearly all cases they are not absolutely perfect.

The last treatment of all for dysmenorrhea should be

hysterectomy and to advocate this is to fail in the treatment of a condition that in most instances can be helped if not completely relieved.

### FUNCTIONAL BLEEDING

Most bleeding of the functional type is due to an ovarian dysfunction and whether the real cause is primary ovarian or primary pituitary is not essential to the understanding of the now known physiology and pathology, and consequently the treatment.

Bleeding accompanied by hyperplasia of the endometrium is the most usual type. In this type of bleeding the uterus or end-organ of the genital tract may be small or large, may contain fibroids or may not. The endometrium in most instances is thick, occasionally polypoid but occasionally very thin. In many instances, microscopically, it shows typical hyperplasia. The hyperplasia is due to either too much estrin or to continuous estrin acting upon it. No progestin influence is present. The ovaries contain a follicular cyst or cysts which are cysts of pathologic physiology and are not neoplastic. These small cysts contain estrin in a greater or lesser amount. There is no evidence of any corpus luteum formation. The pathology of the pituitary in these cases is not known at the present time. The urine of such a patient contains very little or no estrin during the bleeding but after the bleeding has ceased estrin reappears in the urine. The physiology is about as follows: the pituitary being abnormal, produces prolans A continuously; this in turn causes the persistence of a graafian follicle and due perhaps to lack of prolans B, ovulation does not take place. The follicle continues to develop, becomes cystic, and fills with fluid containing estrin. This persistent estrin production causes the endometrium to develop beyond the normal estrin phase and the hyperplasia succeeds the normal proliferative endometrium. As the estrin persists it inhibits the production of prolans A by the pituitary. Then lack of pituitary prolans A in its turn causes a drop in the production of estrin and as estrin diminishes in strength in the cyst sloughing of the endometrium occurs and bleeding takes place. (It is well known that estrin withdrawal is followed by bleeding). The physiology and

pathology of this type of bleeding is known as metropathia hemorrhagica or Shaw, Type I bleeding. The treatment of the condition is obvious. If the cyst could be ruptured the sequence of events would be interrupted; if a luteinizing hormone could be used luteinization of such follicles would follow and the endometrium would change from the proliferative hyperplastic phase to the secretory or corpus luteum phase. Or if a potent corpus luteum hormone could be given in large doses it should change the endometrium to the secretory phase and the later withdrawal of progestin would be followed by menstruation from a secretory phase. (It is now known that if both estrin and progestin are used withdrawal of estrin in the presence of progestin does not allow bleeding but withdrawal of progestin does allow it and it is menstrual [secretory] in type.)

Any method that brought about ovulation in such bleeding cases would be followed by luteinization and thus the normal cycle would be reestablished. It is known that endometrial biopsy and curettage may stimulate ovulation just as copulation with a buck rabbit is necessary for the female rabbit to ovulate. Biopsy and curettage by traumatizing the cervix may be the causal factor in ovulation in these cases and thus be responsible for the return of such cases to a normal rhythm.

The treatment of this condition by means of hormones is not as perfect as it should be theoretically. Estrin by inhibiting the pituitary should stop prolactin A from causing estrin secretion and thus should allow normal events to follow, but such does not seem to be the case. The use of anterior pituitary prolactin, containing as it does some luteinizing factor, should permit luteinization to take place and thus bring about proper changes in the endometrium. It is said to accomplish this in some instances.

Pregnancy urine prolactin, known as the anterior pituitary luteinizing hormone, was considered to bring about luteinization and therefore proper changes in the endometrium, but this is all denied now, as it has been shown that this hormone only causes atresia of the ovary and not luteinization. It does, however, cause theca luteinization and it is possible that this type of luteinization may have some effect on the endo-

metrium. Following the endometrium by means of endometrial biopsy after the use of pregnancy urine prolan is the way to test the efficiency of the method and although in many instances the endometrium does not change, in others a secretory phase has been recognized. It is felt by some that this hormone causes the maturation of a follicle, ovulation, and a corpus luteum formation and thus the absence of many active follicles and corpora lutea in the ovary after treatment is explained. In other words, a single follicle matures as it should and a normal rhythm is brought about. The suggestion of a bleeding factor being responsible is difficult to accept. It is certainly true that in many instances the use of pregnancy urine prolan advocated by the commercial houses and in the doses recommended by them does cause cessation of bleeding and a return to normal. Its use is advised but the exact nature of the physiology is not known.

The use of real anterior pituitary prolan seems more sensible; it may cause the development of follicles and when ovulation follows the cycle returns to normal. Enough clinical experience has not been had to state that this is the best method of treatment but it certainly should be considered and its use is definitely justifiable. Overtreatment might be dangerous because of overstimulation of follicles.

It is conceivable that the use of both pituitary prolan and pregnancy urine prolan in sequence might be of value. The first to cause follicle formation and the second to aid in continuing the follicle on to proper luteinization.

Deliberate rupture of such a persistent follicle would be sound treatment, for interruption of this "middle man" would take pressure off both the pituitary and the end organ, the endometrium. Such treatment would be heroic and although it has been accomplished without disaster to the patient with a cessation of bleeding, it is certainly not advocated.

There are other types of bleeding of functional type and these will be mentioned briefly. At the time of ovulation at the midmenstrual point there is a great congestion of the endometrium and when the estrin level drops, as it does at ovulation, the spilling over of a small amount of blood is often noted. This is a normal process and needs no treatment.

The type of bleeding with a bimonthly rhythm is due to

too frequent ovulation and the exact reason for it is not clear. Too many corpora lutea are found in the ovaries of such patients and though the cycles are too frequent they are nearly normal in character. Inhibition of the pituitary by the use of estrin might help such a condition, and the use of pregnancy urine prolan has been proved of value.

### THE MENOPAUSE

The treatment of the menopause is one of the triumphs of female sex hormonology. At the menopause, whether artificial or natural, certain definite findings are present in the urine and blood. There is a fall in estrin to zero and an increase in the anterior pituitary hormone, prolan A. Hot flashes and nervous phenomena follow ovarian exclusion and they may be extremely severe or mild. Large numbers of hot flashes cause sleepless nights and great embarrassment in the presence of friends. To aid such conditions many advocate the use of bromides and luminal and to a certain extent they are successful. The use of estrin, however, either subcutaneously or by mouth, is miraculous and the well-being of the patient as well as a great reduction in the number of flashes occurs almost as soon as treatment is started. The treatment must be kept up, however, for an indefinite period of time, as it is not accumulative. Slowly the patient finds the correct dose that makes her comfortable and her relief is great. When treating the menopause with estrin the appearance of estrin in the urine is not the most important finding in the successful cases. Drop in the level of prolان in the urine is greater evidence of successful treatment.

The dosage should be from 200 I. U. daily to 6000 I. U. daily, by mouth, and from 1000 I. U. to 50,000 I. U. subcutaneously one to three times per week. The dosage must be worked out for the individual patient but with persistence nearly all women suffering from the menopause can be nearly completely relieved.

### THE HORMONES

The sex hormone of the anterior pituitary gland (prolan) may be purchased as gyantrin and prephysin. The ovarian hormone estrin is for sale under various names—theelin,

theelol, emmenin, amniotin, progynon, progynon B, folliculin, menformon and sistomensin. The ovarian hormone progestin can be purchased under the name of corlutin and proluton. Pregnancy urine prolan (not to be confused with the anterior pituitary hormone prolan) can be purchased as antophysin, antuitrin S, follutein and A. P. L. With this ammunition we should be able to approach any physiologic upset in the female genital tract. Unfortunately all the commercial hormones

~PROLAN~

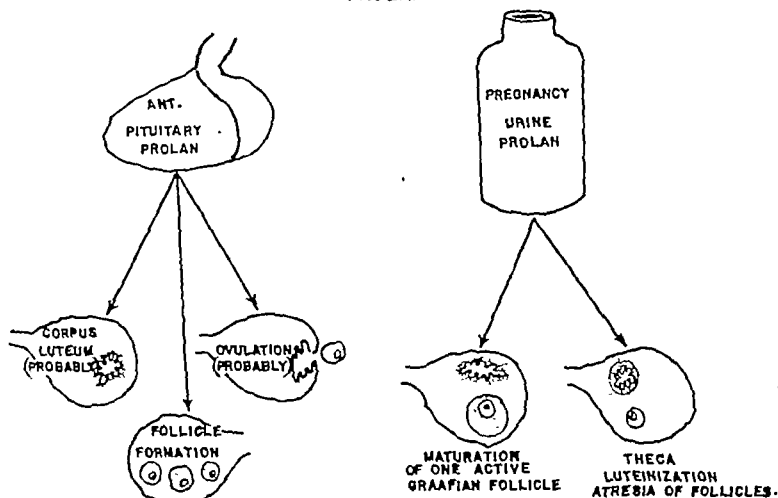


Fig. 170.—The two types of prolan. The anterior pituitary prolan is a stimulator of follicle formation; it causes ovulation and later corpus luteum formation occurs. Pregnancy urine prolan is in dispute. It probably causes the maturation of a fairly well-developed follicle and causes ovulation and luteinization. On the other hand many say that it only causes atresia of follicles and theca luteinization and fails to develop any activity in the ovary at all. These questions must be settled by further investigation.

do not work on humans as they do in the laboratory. There are however certain effects that are of great importance and we can reason our form of treatment from this knowledge. The anterior pituitary sex hormone prolan containing as it does a moderate amount of the luteinizing factor should be able to cause follicle growth and it is reported as doing so in the human. It may only carry the follicle on to full development and not through to ovulation but sometimes this occurs also. If this is true the cases of pituitary failure can be sub-

stituted for and the ovary made to go through its proper cycle, thus cases of pituitary amenorrhea should be helped and successful results have been reported. In cases of menorrhagia where a follicle cyst has been persistent it should be possible to create new follicles one of which might go on to proper ovulation thus relieving certain cases of abnormal bleeding.

Estrin is reported as developing the uterus, as causing hyperplasia of the endometrium, as developing the breast, as changing the vaginal epithelium of children to adult type, and

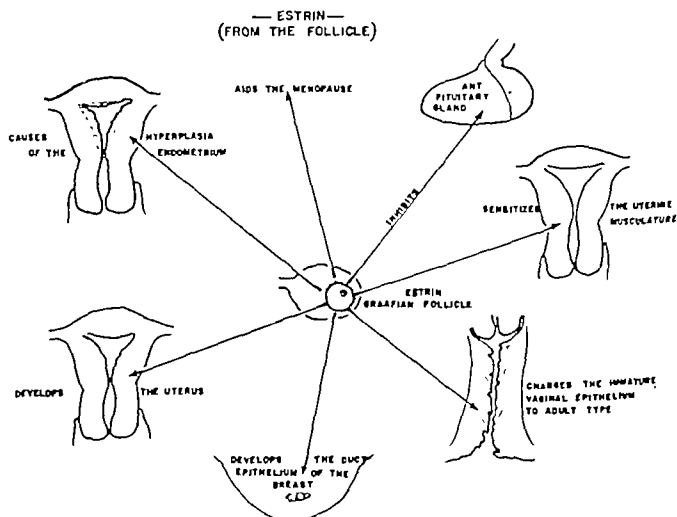


Fig. 171.—Estrin, and by this is meant any of the chemical forms of estrogenic hormones, has various activities. These are diagrammatically illustrated. It is possible that some of these will be proved untrue but for the present the above diagram gives a working scheme.

as stopping hot flashes. Estrin by its inhibiting effect on the anterior pituitary sex hormone should shut this hormone off and prevent the formation of more estrin in the patient's ovary. If this is possible then by judicious use of it and omitting it at the proper time a shortage of estrin can be brought about before the menstrual period. As estrin causes growth of breast epithelium, as it causes premenstrual feelings or molimina, and as it sensitizes the uterine smooth muscle to the oxytocic principle of the posterior pituitary, if it can be relied upon to check pituitary secretion, it should be

able to relieve painful breasts, lactating breasts, molimina, and dysmenorrhea. The methods of using it are described elsewhere in this paper.

Progestin is an unknown quantity at present but if it acts as a neutralizer to estrin and if estrin causes the irritability of the uterine musculature it should be of value in dysmenorrhea (to prevent cramps), in habitual abortion by preventing irritation of the uterine musculature and should aid proper decidualation and nidation. There is some reason to believe it is of help in these conditions. If metropathia hemorrhagica

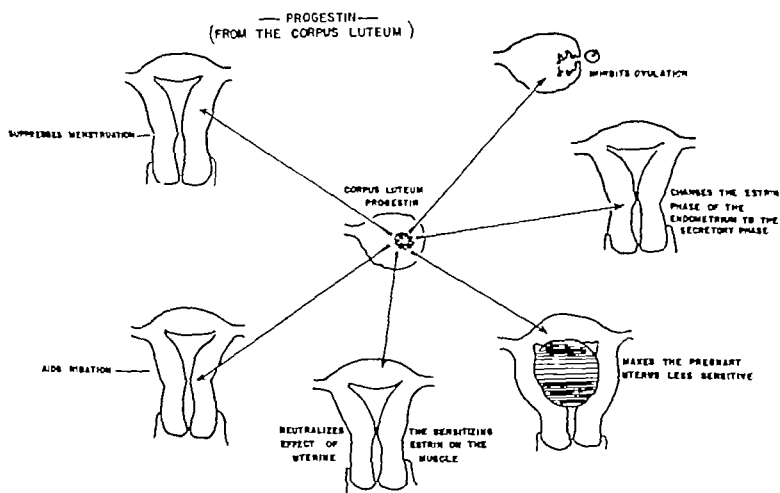


Fig. 172.—The action of progestin from the corpus luteum is diagrammatically illustrated. With this hormone available for use in clinics and practice many of the above actions can be proved or disproved.

is due to continuous estrin production with proliferative endometrium perhaps the use of progestin to change the endometrium to the secretory phase might change the whole picture of this endocrine entity. It is considered the hormone that suppresses menstruation and that withdrawal of it is necessary for menstruation to commence.

The so-called "anterior" pituitary luteinizing hormone or pregnancy urine prolan is now an unknown factor. It was considered that it caused luteinization in the follicles of the ovary and hence changed the endometrium from the estrin phase to the secretory phase but both of these virtues are



denied it. It is now looked upon as acting upon the ovary in a dampening way, causing atresia of the follicles and thus not allowing proper development. It apparently does cause theca luteinization but as normal luteinization is supposed to be due to changes in the granulosa cells and not in theca cells it is difficult to understand its value; perhaps theca luteinization may be as important as granulosa luteinization but this is not known as yet. Pregnancy urine prolan does help abnormal uterine bleeding, it checks the bleeding and occasionally changes are found in the endometrium accompanying the cessation of flow. Sometimes one looks for secretory phases in vain, but as the bleeding is checked by it, all sorts of bleeding factors are hypothesized. This hormone has a definite use in uterine bleeding of the functional type.

Thus as far as the therapeutics of female endocrinology is concerned we are not paupers and in the future there is no doubt but that more knowledge will be added and many of the functional disorders will be classified and properly treated.

## CLINIC OF DR. ABRAHAM COLMES

BOSTON

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### RECENT ADVANCES IN THE TREATMENT OF HAY FEVER AND ASTHMA

#### INTRODUCTION

HAY FEVER and asthma can be considered jointly under one heading, because fundamentally they represent disturbances of a similar nature, one in the nose, the other in the bronchi.

When these two conditions coexist they may be due to the same provocative cause, as noted for instance, in pollen-sensitive patients in whom hay fever and asthma are often provoked by the same pollen, or on the other hand, they may be due to diverse exciting causes. Thus, a patient may have hay fever due to ragweed and asthma due to the ingestion of eggs. Such specificity in the exciting cause of the reaction and such selectivity in the site of reaction, are characteristic of the phenomena of human hypersensitiveness; and it is this hypersensitiveness which in the past has paraded under such diverse nomenclatures as "diathesis," "disposition," "idiosyncrasy," etc., and which has more recently been popularized under its newest adaptation, the term "allergy," that constitutes the fundamental disturbance of which asthma and hay fever are but clinical expressions.

Were we able to correct the fundamental disturbance which permits of the establishment of the hypersensitive state in man and its dependent clinical manifestations, the subject of treatment would be easily dismissed in but few lines. But since this fundamental disturbance is an inherited and integral part of the cellular structure of the body and since all chemical, metabolic and endocrine studies have so far failed to reveal its nature, we must accept it as a fixed and unalterable con-

dition and concentrate on those measures which tend to influence the hypersensitive state clinically. This can be accomplished to a greater or lesser extent in the following ways: by relieving symptoms, by disposing of exciting factors, and by modifying the reactivity of the patient's tissues. Whatever advances have been made in the treatment of hay fever and asthma are directly related to the intelligent application of these measures. This in turn rests upon a clear understanding of the nature and mechanism of hay fever and asthma, and above all upon a correct diagnosis. Hence it is necessary, in the course of our discussion, to dwell upon these phases, even at the risk of digression.

#### DIAGNOSIS\*

If the patient happens to be seen in the attack, the diagnosis of hay fever or asthma is self-evident. The characteristic spasmodic sneezing of the former and the audible spasmodic wheezing of the latter, readily suggest the nature of the ailment. Certain differential possibilities, however, must be borne in mind. Hay fever may be simulated by the common cold, by a foreign body in the nose and by polypoid degeneration of the nasal mucosa, in all of which, sneezing, nasal stuffiness and rhinorrhea may be present. These conditions, however, lack the itchy nose, palate, and eyes, which are so characteristic of vasomotor rhinitis and the strict seasonal incidence of symptoms when pollens are the causative agents.

Asthma must be differentiated from a number of other conditions which are accompanied by continuous or intermittent attacks of dyspnea. The nocturnal dyspnea of the failing heart is characterized by a history of progressive shortness of breath, by evidence of congestion in one or both bases and by the patient's favorable response to digitalis and morphine. The asthmatoïd breathing which often accompanies acute coronary thrombosis comes in the wake of an acute anginal pain, a symptom foreign to the asthmatic state. The stertorous and labored breathing, caused by a foreign body in the bronchi is differentiated from true asthma by its sudden onset and occurrence in a previously well patient, usually a

\* The term "hay fever" is used interchangeably with vasomotor rhinitis, for the former is merely a special variety of the latter.

child. The dyspnea that may accompany an enlarged thymus, an aortic aneurism, a pleuritic or pericardial effusion or pressure upon bronchi from mediastinal tumors, is different from the spasmodic breathing of true asthma, with its prolonged expiratory phase, the scattered rhonchi in the chest, the elevated shoulders, fulness in the neck and dependent position which the patient assumes to facilitate respiration. And yet bronchial asthma may coexist with myocardial disease, coronary sclerosis and all other conditions enumerated above. In such instances treatment must be directed toward the amelioration of the coexisting conditions as well, lest our attempt to treat the asthma may fail.

When seen between the attacks, in a symptom-free period, the situation is somewhat different. Here the history of the case is vital. The following points, when elicited, will enhance the possibility of a correct diagnosis:

1. The spasmodic nature of the attack with freedom of symptoms in the interim, especially so in the early cases. In the chronic type, symptoms in a milder form may persist throughout.
2. A tendency to periodicity, the attacks occurring sometimes either spring or fall, or sometimes on week-ends, or during the catamenia in the female, or only during the early morning hours.
3. An incidence in the patient of other manifestations of allergy, such as, eczema, urticaria, migraine.
4. A family history of allergy.

The physical examination during a symptom-free period is not helpful, but a high eosinophile count will emphasize the probability of an existing hypersensitiveness—the fifth characteristic of the allergic state.<sup>1</sup>

While such data, when obtained, are strongly suggestive of the nature of the disease, there is another phase to be considered in the diagnosis, viz.: the "exciting factor."

Reference has already been made to the hereditary nature of the fundamental disturbances which permits of the establishment of sensitization in man. The acquisition, however, of the specific sensitivity is not governed by heredity, but by the mere chance of exposure to a variety of substances which, when inhaled or ingested, tend to sensitize the susceptible in-

dividual. Subsequent exposure to the specific substance may result in asthma or hay fever. Hence the history of the case must also deal with the influence of occupation, location, environment and seasonal variations on the patient's symptoms. Examples of these are to be found in bakers who are sensitive to flour, in grooms who are sensitive to horse dander, in druggists who sneeze or wheeze from the inhalation of lycopodium or acacia, in the hay feverite who suffers only during the pollination season and in the traveling man who loses his symptoms when he sleeps away from home, thus escaping from some environmental dust. In other cases the exciting factor is not so obvious and here an exhaustive survey of the case, which may be completed only during several visits and only with the cooperation of an observing patient, is most important. A few examples will be illustrative:

**Case I.**—A thirty-five-year-old woman residing some 60 miles out of town came in with a history of seasonal "hay fever" and asthma of several years' duration, lasting from June to the end of September. The history was suggestive of pollen disease, since her symptoms concurred with the pollination period of grasses and ragweed. (N. E. states.) Skin tests with all the indicated pollens proved negative. On further questioning it was discovered that the second floor of her house, which was not occupied during the winter, was used for the accommodation of tourists during the summer months. Her symptoms began the early part of June, as soon as she started cleaning the upper floor, and ceased about the end of September, when the influx of tourists ceased and the upper floor was closed again. On a subsequent visit tests were done with extracts from samples of floor dust and bedding from the upper floor and huge reactions were obtained to most of them. By avoiding the upper floor, this patient remained symptom-free throughout the past summer. In this case without a history, the causative agent would have been missed and treatment, therefore, unsatisfactory.

**Case II.**—A farmer, aged twenty-eight, came in complaining of perennial asthma with aggravation of symptoms from the middle of August to frost. He knew he was "sensitive to horses" but his asthma persisted even when some distance away from the stable. Skin tests were positive for horse dander and also for ragweed. The latter probably accounted for the aggravation of his symptoms during the fall. On further questioning it was discovered that his asthma was also worse whenever he fed the cows. Skin tests with cow dander were negative but he gave a striking reaction to an extract of cow fodder. He then remarked that whenever he spilled the fodder out of the bag he would choke up badly, but he attributed this aggravation of symptoms to effort. Any other effort, however, failed to aggravate his asthma to the same extent. He has avoided contact with cow fodder and his asthma has improved since. Here again, no progress could have been made without a complete history.

**Case III.**—A girl of seventeen was brought in because of perennial "hay fever" of one year's duration. Skin tests with the most likely offending proteins

were negative. On further questioning we learned that the patient moved to her present residence some eighteen months ago. In back of her house was a leather-finishing establishment where in the process of shaving or "skiving" a lot of leather dust was created. The landlord who lived on the lower floor of the house, was also the owner of the leather shop, and invariably, upon return home from work, would shake his clothes in the corridor, thus disseminating the leather dust throughout the house. At my request, a sample of the leather dust was brought in and extracted, but when tested on the patient's skin, it failed to produce a reaction. Intranasal tests were then resorted to and when a pledget of cotton soaked in the leather extract was inserted into the patient's nose, her "hay fever" was reproduced within ten minutes. None of the controls gave evidence of any such reaction. Subsequently the patient remembered that on a prolonged visit to her uncle, some 40 miles away, she was symptom-free and that upon return home, her symptoms recurred. Needless to say that the history alone led to a correct diagnosis, which, after all, is the backbone of successful treatment.

When we consider the countless substances to which one is exposed in his daily life at home and occupation, and that each substance under suitable conditions can become a sensitizer, one appreciates the difficulty of "spotting" every possible exciting factor. Fortunately, however, experience has taught us that in the majority of cases the exciting cause of the disease is to be found in the patient's immediate environment and in his usual dietary and within this sphere our efforts should be expanded, always of course, bearing in mind broader and more distant possibilities. While the search for the exciting factor is often determined through the history of the case alone, in many instances it may be facilitated by the application of the protein sensitization tests.

#### TESTS FOR HYPERSENSITIVENESS

**The Direct Method.**<sup>2</sup>—The mechanism of the "protein" sensitization test is based upon the reaction which takes place when the specific substance or allergen meets its corresponding specific antibody or reagin. In the case of hay fever or asthma, a similar reaction takes place in the nasal or bronchial mucosa, where it causes edema, and in the smooth muscles of the bronchi, which are thrown into spasm. The most logical method, therefore, of testing for hypersensitiveness, would consist of bringing the suspected substance, or an extract of it, in direct contact with the sensitized tissue, and the resulting reaction observed. This is exactly what was done in the leather-sensitive case described above. There are several dis-

advantages, however, attached to this direct method of testing:

1. The technic is difficult, especially when it comes to introduce the suspected substance into the bronchial tree.

2. One is never certain of the extent of the patient's tolerance for the specific substance and an overdose instilled into the bronchi may result in a severe reaction, even to the point of endangering life.

3. Not more than one or two tests can be done during a single visit.

And yet the direct method of testing proves useful when no reactions to the suspected substance can be obtained by any other methods. To illustrate further:

**Case IV.**—Miss S. D. has had a persistent cough accompanied by tightness in the chest, of about one year's duration. The history suggested hypersensitiveness as the basis for her trouble. Skin tests with the routine proteins were negative. Further questioning indicated that orris powder might have been the important offender. This the patient was loath to believe, especially in the absence of a positive skin reaction to orris. I then asked her to lend me her powder compact and submitted myself to the inhalation of a thick powder dust created by shaking the puff. Miss D., impressed by the harmlessness of the procedure, submitted herself to a similar exposure with the result that a most distressing attack of cough and asthma followed within a few minutes. The patient, convinced of the effect of powder on her bronchial tree, has given up its use and was "cured." (How simple the treatment can be at times!)

Such a procedure, though drastic, is often needed to prove the point. What is true of orris powder is also true of most any sensitizing substance which can be instilled or insufflated into the patient's nose or bronchial tree. Fortunately, the direct method of testing is not often indicated.

**The Skin Test** is usually satisfactory. In most instances the patient's skin is involved in the process of sensitization, so that when the suspected protein, in solution, is applied to the scarified skin, a local reaction occurs with whealing, erythema and itching, thus resulting in the so-called "positive" *scratch test*.

When is a skin test positive? Generally a skin test is positive only in relation to other negative tests. A wheal of from 3 to 5 mm. with a surrounding erythema of 8 to 10 mm. is positive if all other tested sites fail to react at all. On the

other hand, if one or two substances produce a wheal of 10 to 15 mm. with a surrounding erythema of 20 to 40 mm., the smaller reactions are only suggestive. Finally, the skin may be irritable and all tests, including the saline control, may react. In such case they are all negative.

Of late this protein skin test has been widely exploited, without due regard to the fact that a positive skin reaction is not always indicative of the cause of the patient's trouble, while at the same time some other nonreacting protein may be at fault. Recent studies<sup>3</sup> have indicated that in asthma 40 per cent of the skin-reacting proteins and in perennial hay fever (or vasomotor rhinitis) only 25 per cent are accountable for the patient's symptoms. In seasonal hay fever, the positive skin reactions are accurate in close to 100 per cent. These observations should discourage one from laying too much stress on the skin test alone, but rather utilize it as an adjunct in determining the specific cause of the patient's symptoms.

When by the simple scratch method we fail to obtain a positive reaction to the suspected substance, we may resort to the more delicate *intradermal method of testing*. This is done by injecting the specific extract\* in suitable quantity and concentration between the layers of the patient's skin. When positive, a characteristic local reaction with whealing and erythema occurs. While the intradermal method of testing is more "sensitive" than the scratch method, it is also more irritable to the skin and may be productive of many false reactions. Hence its use should be limited to those cases whose "scratch tests" are negative.

Incidentally, a practical and simple method of skin testing consists of soaking the suspected agent in decinormal sodium hydroxide and applying it, *in toto*, to the patient's scarified skin, preferably on the back.<sup>4</sup> Positive reactions may thus be obtained to a variety of environmental substances, such as rug dust, stuffings from bedding, furniture, etc., and subsequently their clinical importance determined.

The ophthalmic test,<sup>5</sup> the passive transfer of Prausnitz and Kustner,<sup>6</sup> the Leucopenic index of Vaughan<sup>6</sup> and the homely method of trial and error, are additional tests for hypersensi-

\* Protein extracts for intradermal use may be obtained from several biological houses.



tiveness. Elimination diets will be referred to again, but space does not permit the discussion of other tests in detail.

The question often arises as to how many proteins should a patient be tested with?\*

 The commercial houses put out over 400 protein extracts, altogether too many for the average case. And yet, when one considers the countless substances to which a patient may become sensitized, 400 are too few. Hence, the question should be put: what proteins should a patient be tested with? The answer to this is in the history of the case. Take an account of the patient's occupation, home environment, dietary and the season when his symptoms occur, and then test him with the indicated proteins. Sixty to 80 food substances more than cover the average dietary. But if the history brings out the patient's fondness for duck eggs and turtle soup, test him also with these two foods. Tests with 10 to 15 household allergens are ample for the average case, but if the patient happens to be a chemist and gets his attacks only when in the laboratory, test him with all the chemicals to which he is exposed. In pollen sensitive cases, skin tests should be done with the prevailing pollens of a given locality, a familiarity with which is essential. Generally, one is to remember that the trees pollinate in the spring of the year (March to June), the grasses during the summer months (June and July) and the weeds during the fall (August and September).

#### OTHER ETIOLOGIC CONSIDERATIONS

While in the main hay fever and asthma may be looked upon as manifestations of human hypersensitiveness, there are instances where such a background cannot be demonstrated. Here a family history of allergy may be lacking and skin tests may all be negative. The symptoms are generally referable to some reflex irritation or to infection. Reflex asthma may be produced through irritation of the sphenopalatine ganglion (asthmogenic area) in the nose or through a pansinusitis or through stimulation of the vagus through any of its numerous branches, such as cardiac or intestinal. It is generally accepted, however, that reflex symptoms occur only

\* See Appendix I.

in such individuals in whom hay fever or asthma has been previously established through some specific cause.

The rôle of infection in the causation of hay fever and asthma is important though its *modus operandi* is speculative. Some observers uphold the view that infective vasomotor rhinitis and infective asthma<sup>7</sup> are distinct clinical entities wherein bacteria first act as sensitizers and subsequently upon reinfection, as exciting allergenes. Others maintain that bacterial infections lower the threshold of the patient's tolerance for some extrinsic allergen which only then becomes operative and provokes symptoms. Clinical examples which uphold the latter view are numerous. Thus a cat-sensitive patient may be free of symptoms except in the course of a cold, when asthma would set in. A similar cold, in the absence of the cat, does not provoke any asthma. Here infection acts as a nonspecific or as an intermediary cause, which, nevertheless, must be reckoned with seriously, for it stresses the importance of intermediary factors in the causation of respiratory allergy in general. Anything that upsets the patient's physical or mental equilibrium may act as such an agent. On these grounds it is thought that such diverse causes as indigestion, pregnancy, fatigue, constipation, endocrine and metabolic disturbances and even emotional strain, may provoke characteristic symptoms of hay fever or asthma in the susceptible individual. Once a relationship has been established between fatigue and asthma, constipation and asthma, colds and asthma, etc., the symptoms may recur either through a toxic irritation of the neurocirculatory system or on the basis of conditioned reflexes,<sup>8</sup> unless the chain of continuity is broken. Aside from the fact that intermediary agents are capable of provoking symptoms, they often become real complications of hay fever and asthma. Especially is this true of infection. Whether bacterial infection acts as a direct specific cause or as an indirect intermediary cause, sooner or later it tends to dominate the picture in the form of chronic sinusitis, bronchitis or bronchiectasis. As a result of chronic infection, definite and irreversible tissue changes take place in the nose or bronchi, so that symptoms may continue even though the primary exciting cause has been eliminated. Most obvious are these changes in the chronic asthmatics, where advanced

emphysema and secondary cardiac complications dominate the picture. This group of patients taxes the ingenuity of all of us and contributes considerably to our failures.

### TREATMENT

As pointed out in the introduction to this communication, our aim in the treatment of hay fever and asthma is to modify the hypersensitive state clinically. We shall now consider the various measures by which this can be accomplished.

**Relief of Symptoms.**—The most important remedy at our disposal is adrenalin. It is a sympathetic stimulator and tends to produce vasoconstriction and to overcome bronchial spasm. Three to 8 minims injected subcutaneously or 1 to 2 minims, intradermally, will relieve asthma of average severity and will influence favorably an attack of hay fever. If no relief follows, the dose may be repeated within twenty to thirty minutes. When no response follows repeated subcutaneous doses of adrenalin, the needle may be inserted into the cubital vein and kept there while 1 minim of adrenalin chloride 1:1000 dilution is injected directly into the circulation at three to five minute intervals, until relief is obtained. This may be followed by  $\frac{1}{12}$  grain of morphine sulphate or a corresponding dose of pantopon, to secure mental relaxation and a prolonged effect of adrenalin. While large doses of morphine are contraindicated in asthma because of their depressant effect on the respiratory center, small doses ( $\frac{1}{12}$  or  $\frac{1}{16}$  grain) are indispensable and where all other measures fail, morphine sulphate, judiciously used, is often the remedy of choice. Not infrequently hypersensitiveness to morphine exists and this is the one serious contraindication to its use. Whereas an attack of hay fever can always be relieved with the aid of adrenalin, ephedrine, morphine and atrophine, asthma occasionally becomes intractable and may persist in spite of all efforts at relief. Such cases, though infrequent in occurrence, are so important and trying that at a recent meeting of the Society for the Study of Asthma and Allied Conditions, the management of intractable asthma<sup>o</sup> was freely discussed from the floor. The following measures were suggested as worthy of trial in any individual case:

1. Phenobarbital sodium, 2 grains, subcutaneously.
2. Subcutaneous normal saline (in a case of intractable asthma with persistent vomiting).
3. Colonic administration of ether in oil (patient in collapse).
4. Sedation in addition to adrenalin.
5. Oxygen tent.
6. Sodium amytal, intravenously.
7. Caffeine sodium benzoate, subcutaneously in  $7\frac{1}{2}$  grain ampules, every fifteen minutes for 3 to 4 doses, or caffeine citrate, 5 to 7 grain doses by mouth.
8. Apomorphine,  $\frac{1}{120}$  grain with 1 to 2 grains of codeine and 8 to 10 minims of adrenalin made up together and one third of this administered every five to ten minutes.
9. Sodium iodide (31 grains) intravenously.
10. Morphine and atropine.
11. Two to 3 ounces of whiskey several times a day if needed.

An additional and relatively new method for the relief of intractable asthma is by the continuous intravenous administration of glucose-adrenalin. This procedure consists of administering 5 per cent glucose with a 1: 200,000 adrenalin solution, intravenously, by the constant drip method. In one such recent case where adrenalin, oxygen, morphine and ether failed to give sufficient relief, this solution was administered continuously for thirty hours with complete cessation of symptoms. The flask containing glucose and adrenalin connects to a sensitive valve which permits of a fine adjustment in the rate of flow of the solution in accord with the patient's needs. In our case, 20 drops per minute proved most efficient. By this method, the patient is provided with fluids, calories and adrenalin at one time. A good deal of discomfort arises to the patient from keeping the arm stretched out and fixed on a board to avoid dislocation of the needle, but the intractable asthmatic will accept this instead of the mortifying dyspnea.

There are instances where the response to adrenalin, though favorable, is evanescent, so that a dose may be needed every hour or two. This is particularly unpleasant during the night because it interferes with sleep. In such cases we found a

mixture consisting of three parts of adrenalin and one part glycerin, altogether 2 cc. when injected subcutaneously (with a  $1\frac{1}{4}$  inch 25 gauge needle) will give a less rapid but more prolonged adrenalin effect. (The addition of  $\frac{1}{4}$  of 1 per cent nupercain relieves the pain caused by the injection of glycerin-adrenalin). In fact, I have often given 1 or 2 minims of adrenalin intracutaneously for immediate relief and followed this by 2 cc. of glycerin-adrenalin for its prolonged effect. The chief disadvantage of this method lies in the painful local irritation produced by the glycerin fraction.

*The inhalation of adrenalin chloride 1:100 concentration* for the relief of an asthmatic attack has recently been described by Rowe. The author recommends a specially constructed whole glass nebulizer for this purpose.\* A very gratifying feature of this method is that the patients obtain relief without the immediate aid of a physician and without the use of a hypodermic needle and long before the full physiologic effect of adrenalin on the circulation, such as tremor, palpitation and pallor, becomes evident.

**Ephedrine.**—This drug is quite similar to adrenalin in its physiologic effect, though slower in action. It is effective when given orally in  $\frac{3}{8}$  or  $\frac{3}{4}$  grain doses. When used alone or in conjunction with potassium iodide it is of greatest benefit in the subacute type of asthma. A dose of ephedrine taken in time will often abort a threatening attack. In hay fever, ephedrine is useful when taken orally or applied locally in the form of a spray or jelly. Ephedrine when taken internally may cause restlessness, tremor, sleeplessness and occasionally painful urination in the male. These effects may be partly overcome by combining ephedrine with some sedative. Ephetonin,<sup>10</sup> a synthetic ephedrine preparation, is said to be less toxic, though fully as efficient. A volatile synthetic ephedrine preparation marketed as Benzedrine Inhalant will often palliate an attack of sneezing, though it is ineffective in asthma.

Hypertension, when it occurs in asthma, is no contraindication to the use of either adrenalin or ephedrine. In fact, with the relaxation of bronchospasm, the blood pressure tends to fall.

\* The atomizer may be obtained from the Peralta Hospital, Oakland, Calif.

Of the older remedies which still maintain their traditional importance in the treatment of asthma, are stramonium, chiefly in the form of asthma powder, and the iodides. While the former is used mainly in aborting an acute attack of asthma, the latter are more useful in the subacute or chronic stages. The action of iodide is probably systemic as well as local on the bronchial mucosa. Ten minims of the standard solution of potassium or sodium iodide will ease expectoration and reduce dyspnea in a great majority of cases. Although the iodides are readily absorbed through the intestinal tract, they sometimes exert a more beneficial and more rapid effect when administered intravenously. For this purpose sodium iodide in 2-Gm. doses (20 cc. ampule) is available commercially. One, two or even three ampules may be administered within twenty-four hours in stubborn cases.

When the acute attack is over the patient may become either entirely symptom-free and need no further treatment or the presence of chronic bronchial or sinus difficulty may become evident. In either case an exhaustive physical examination including rhinologic, cytologic, roentgenologic and urinary studies are important. An existing pansinusitis, whether it complicates hay fever or asthma, needs surgical interference. The principle underlying such treatment is the removal of diseased tissue and the establishment of ample drainage. In no way, however, must such treatment be aimed at the relief of the underlying disturbance, although incidentally, the patient's outlook for an "ultimate cure" is better in the presence of healthy nasal chambers. In this regard, Weille's studies<sup>11</sup> are interesting. Out of a group of 40 asthmatics operated on for pansinusitis, only 12 per cent have had complete relief of symptoms for variable periods of time.

x-Ray examination of the chest will exclude a coexisting tuberculosis, large tracheobronchial glands, pleural effusions, pulmonary tumors, foreign bodies in the bronchi, all of which may tend to complicate the asthmatic state. Most important of all are bronchiectasis and atelectasis, which constitute the most common, and most serious complications of asthma. The former is due to bacterial infection, which thrives well in the poorly aerated peripheral bronchial bed, while the latter is due to the plugging of a bronchus with thick mucous secretions

causing collapse of the corresponding portion of the lung. On reexamining patients with chronic asthma, one often notes an absence of breath sounds over a given lung area, which may "clear" suddenly after a coughing spell or within twenty-four hours. At the same time another portion of the lung may become atelectatic.

For the relief of bronchiectasis complicating asthma, postural drainage is the measure of choice. The patient leans over the bed, his hands reaching the floor, and forces himself to cough for a period of three to five minutes. The procedure should be repeated two or three times a day and continued for months. While "cure" is out of the question, relief of symptoms with diminution in the amount of sputum are common following this procedure. Ammonium chloride, T. I. D. in 3 grain doses, will help to liquify the sputum. Recently<sup>12</sup> postural drainage has been suggested in all asthmatic patients on the basis of relieving the "accompanying bronchial and pulmonary exudate."

For atelectasis, the treatment of choice is removal of the plug of mucus through a bronchoscope. This procedure, though unpleasant for the patient, is not dangerous, and is often extremely helpful. Such treatment, however, should not be used promiscuously. The patients should be carefully selected and at the same time should be subjected to a bronchography with lipiodol for further diagnostic details. In fact, repeated lipiodol instillations without bronchoscopic drainage have been suggested as a therapeutic measure in infected asthma. This is not, however, an accepted method of treatment.

Cytologic and urinary examinations may divulge a co-existing blood dyscrasia or a kidney affection, the correction of which will enhance the possibility for better results in the management of asthma or hay fever.

The status of the "heart in asthma"<sup>13</sup> is still clouded with uncertainty. Logically, the right chamber should suffer because of the increased resistance to the pulmonary circulation in asthma and its frequent concomitant emphysema. x-Ray and electrocardiographic studies, however, fail to substantiate such an assumption. As to dyspnea on effort, the most important symptom of cardiac embarrassment, this is so obscured

by the pulmonary dyspnea incident to the asthmatic state, that the two cannot be differentiated. And yet, a daily dose of  $1\frac{1}{2}$  to 3 grains of digitalis in the older patient with asthma, with feeble and rapid pulse, may be of some benefit. Cardiac irregularities, when they occur, must be treated without regard to the coexisting asthma.

**The Treatment of the Exciting Cause.**—The next step in the treatment of hay fever and asthma is concerned with an allergic survey of the patient. Reference has already been made to the importance of the history in determining the nature of the exciting factor. In this regard, the patient's environment, occupation and dietary have been particularly stressed as the most common sources of trouble. A critical analysis of the skin test has been briefly presented. When neither the history of the case nor the skin tests prove helpful in determining the nature of the exciting factor, the following measures may be resorted to both for diagnostic and therapeutic purposes:

1. *Change of Environment.*—To this end, hospitalization is the procedure of choice. In the absence of such facilities, a change to a friend's or relative's home for a week or two may be helpful. Sometimes a change to a different bedroom, even in the same house, may bring about gratifying results. Relief thus obtained points to the environment as the source of trouble. Upon reentering his home, however, the patient's symptoms may recur. Hence a systematic course of "allergic cleanliness" should be instituted before allowing the patient to reenter his old habitation.

2. *Allergic Cleanliness.*—Allergic cleanliness differs from general "household cleanliness" in that the latter is directed toward the removal of dust, while the former is aimed at the elimination of its source. Experience has taught us that bedding, overstuffed furniture and rugs are the most common sources of active household allergens. Hence the mattresses and pillows should be either changed or encased in rubberized, dust impermeable cloth, while comforters should be substituted by freshly washed blankets. Recently a liquid rubber (Vultex\*)<sup>24</sup> has been suggested as an efficient agent for protecting pillow and mattress against dust emanation. A coating

\* Vultex Chemical Company, 660 Main Street, Cambridge, Massachusetts.



of Vultex is applied with an ordinary brush and allowed to dry overnight. This seals the bedding and makes it dust proof. Rugs and overstuffed furniture should be removed from the patient's bedroom. Closets are dust collectors, hence they should be whitewashed and only freshly cleansed clothing be kept there. Furnace registers are apt to bring in a good amount of cellar dust, hence they should be covered with muslin, which acts as a partial filter. Perfumes, powders, disinfectants, deodorants, moth-killing sprays, are common offenders and should not be permitted in the patient's room. Whatever is washable, such as curtains, draperies, bedspreads, may be left in the room with impunity.

The living room furniture, next in importance, as a dust producer, cannot be handled with the same ease as the bedding. Efforts should be made to obtain samples of stuffing from the divan, chairs, rugs, etc., and each sample should be soaked in decinormal sodium hydroxide and tested on the patient's skin. In the presence of a positive reaction, the stuffing should be changed or the furniture eliminated. When this is impossible, the patient should remain in his own room for comfort. Sun parlor furniture and overstuffed scatter chairs are all possible sources of trouble and should be handled in like manner.

The kitchen is usually least troublesome of all rooms, except for the presence of dusting powders and baking powders, which may be offensive to the patient. Usually, however, the patient is conscious of the ill effects of such products and tries to avoid them. A mouth and nose mask, consisting of 10 layers of gauze and worn while dusting or washing, will act as an efficient filter.

The bathroom should be kept clear of powder and perfumed soaps. Tooth powders and pastes often contain orris root, a common offender, hence, it is my practice to substitute these with common table salt for a trial period.

These measures, in brief, constitute "allergic cleanliness."

3. *Elimination Diets*.—Rowe's elimination diet<sup>15</sup> may be instituted at the same time with allergic cleanliness. A trial period of seven to ten days is ample to determine the effects of each diet on the patient's symptoms. If no relief is obtained within that period, foods are not likely offenders. An-

other form of trial diet consists of limiting the patient to one type of food, such as milk, for a period of three to five days. If improvement follows, additional foods are given each subsequent day, until the "offender" is determined. Where sensitivity to milk is suspected, beef broth or thin gruel with maple syrup may serve as the initial food. (See appendage II.)

**Desensitization.**—In a good many cases the exciting allergen is elusive, in others, though found, it cannot be eliminated, as often is the case in pollen-sensitive patients or in the occupational allergies. In such instances we must resort to the *third method of treatment*, viz.: an attempt to change the reactivity of the patient's tissues by desensitization. Desensitization may be *specific*, when the treatment is carried out with an extract of the offending substance, or it may be *nonspecific* when any shock-producing agent, such as milk, pepton or tuberculin is injected into the patient parenterally.

**Specific Desensitization.**—Any substance which is causative of the patient's symptoms and which produces a positive skin reaction, can be utilized for specific desensitization. The first step in desensitization is to establish the extent of the patient's tolerance for the indicated allergen. In the case of pollens, a concentration of 1: 50 can be purchased from any of the several commercial houses and dilutions of 1: 500, 1: 5000, and 1: 25,000, prepared with saline under sterile conditions. Some biological houses offer the pollens already prepared in the various dilutions. The patient's forearm is then cleansed with alcohol and a drop from each of the pollen dilutions is placed over its anterior surface. Using a fine scalpel or the sharp point of a needle, each site is gently scarified, always starting with the weaker dilution and working up to the most concentrated one. Within twenty to thirty minutes a characteristic reaction with whealing pseudopod formation and surrounding erythema will appear. The more concentrated the extract, the stronger the reaction, so that the weaker dilutions of 1: 5000 or 1: 25,000 may fail to react at all. Treatment is then instituted with that dilution which fails to produce any appreciable reaction. 0.10 cc. of such a dilution is a safe initial dose. If the local reaction from the first dose does not exceed the size of a silver dollar, it is safe

to increase the following dose by 0.10 cc. And so each subsequent dose is estimated by the extent of local reaction from the preceding one. An extensive swelling at the site of injection always calls for a repetition or even a diminution of the previous dose. The change from a weaker to a stronger dilution must be exercised with a great deal of care and caution. While there are no fixed rules for this procedure, the following suggestions may be accepted as a working basis:

If the last dose is 0.4 cc. of 1: 25,000 dilution, the next rose may be 0.1 cc. of 1: 5000 dilution.

If the last dose is 0.9 cc. of 1: 5000 dilution, the next dose may be 0.1 cc. of 1: 500 dilution.

If the last dose is 0.9 cc. of 1: 500 dilution, the next dose may be 0.1 cc. of 1: 50 dilution.

As to the number of doses needed in each case, no one can venture to guess, for each patient is a "case unto himself" and his needs are determined by the severity of his symptoms, by the average concentration of pollens in his district and above all by his inherent response to treatment. The first year of pollen treatment is the trial period and the patient should be informed about this at the outset, so that a poor result may not reflect unfavorably on the physician nor on the method employed in treatment.

The aim in pollen therapy, and for that matter in all therapy by desensitization, is to raise the patient's tolerance for the given allergen, to a maximum. In one case it may take 10 pollen doses, while in another 50 pollen doses, to accomplish the same results; moreover, the final or optimal dose may in one instance be 0.1 cc. of 1: 500 dilution, while in another a whole cubic centimeter of 1:50 concentration. Hence, it is fallacious to undertake such therapy with any performed schedule of "doses."<sup>16</sup> One must "feel his way in the dark" and forge ahead cautiously and wait for the appearance of the pollen season to decide on the efficacy of the treatment. Granted that the patient has been brought up to his maximum level, that attempts to further increase the dosage meet with obstinate resistance in the form of large local reactions or even constitutional reactions, does it mean that the patient will have desired relief the coming season? In a large percentage of cases, yes, but in the others relief may be slight or nil. It

is these poor results in pollen therapy that bother us a lot, and so far no one has ventured a final word as to their cause. It is generally accepted, however, that failure in pollen therapy may be due to insufficient treatment, to the existence of additional sensitivities, to structural intranasal abnormalities, to coexisting nutritional disturbances or to an inherent refractoriness of the tissues to therapy. A search for all such factors, and where possible, their elimination or correction may bring about better therapeutic results in the future. At all times, however, it is well to bear in mind that desensitization in man is a *relative* and not an *absolute* procedure and that a heavy pollen season invariably means a larger number of poor results.

There are four generally accepted methods of desensitization. We shall consider them in order of their importance:

1. *Preseasonal Method*.—Here the treatment is instituted four to six months before the expected date of pollination and doses are given at weekly intervals. With the onset of the season, the last dose may be decreased one third and repeated at seven to ten day intervals to the end of the season. If a patient proves resistant to treatment, smaller but more frequent doses may be given at three to four day intervals. An overdose after the onset of the season may precipitate severe and persistent hay fever.

2. *Perennial Method*.<sup>17</sup>—At the completion of a season's treatment, the final dose may be maintained throughout the following nine months at four-week intervals. By this time, a change to fresh pollen extracts will necessitate a diminution in dose and from then on the treatment is again continued with increasing doses to the point of maximum tolerance. Not all patients, however, so treated can maintain a fixed tolerance so that after the third or fourth month the local reactions may become large and consequently the dose has to be reduced. After two or three years of perennial treatment, a fairly stabilized tolerance for a higher concentration of the pollens becomes established and only at this time are the results almost invariably satisfactory. A serious disadvantage of this method is the need of constant visits to the doctor throughout the year, which is often depressing to the patient.

3. *Coscasonal Method*.—This is applicable in those cases

who first come for treatment after the onset of symptoms. Here, the daily administration of small doses of pollen extract with the addition of 0.25 cc. of stock catarrhal vaccine every fourth or fifth day is apt to give the patient some relief. Again it should be remembered that an overdose at this time may precipitate most severe and lasting symptoms.

4. *The Rush Method*.<sup>18</sup>—A few days before the expected date of pollination the patient is placed in the hospital under close supervision and is given small though increasing doses of pollen at one or two hour intervals. This procedure is repeated for several days and the patient discharged. Though good therapeutic results are claimed for this method, the rapid cumulative effect of the pollens with a possible resultant constitutional reaction nullify its advantages.

Constitutional reactions are best treated by preventing them. This can be accomplished by carefully estimating the indicated dose and by avoiding the injection of pollen directly into the circulation. When it occurs, the constitutional reaction is combated by placing a tourniquet *above* the site of inoculation and by administering adrenalin in sufficiently large doses to overcome the symptoms. I have found that a tight elastic placed above the point of inoculation will retard the absorption of pollens and lessen the tendency to constitutional reactions. This is particularly indicated in patients who are highly sensitive to pollens.

Whatever has been said in regard to pollen therapy is equally applicable to the use of any other allergenic extract for desensitization in either hay fever or asthma. Since the allergenic potency in some substances is more active than in others, it is important to carry the dilutions high enough even to 1:1,000,000, in order to obtain a safe initial dose for therapy.

**Nonspecific Desensitization.**—Any substance which, when injected parenterally, produces a general reaction in the body, tends to alter the reactivity of the tissues to specific irritants. While the mechanism here involved may actually stimulate the immune processes in the body it is, nevertheless, nonspecific in that the therapeutic results are related not to the substance injected, but to the reaction it produces. Thus, milk, blood serum, whole blood, pepton, sulphur in oil, tuber-

culin and vaccines are commonly used for the production of such reactions. Although the response to such treatment in hay fever and asthma is variable, the procedure is nevertheless justifiable, when other measures fail to produce results. Of the several shock substances suggested for use, milk in 10 cc. doses, 1 to 5 per cent pepton in 1 cc. doses and whole blood withdrawn from the patient's cubital vein and reinjected into the buttocks in 10 cc. doses, are commonly employed. Intravenous injections of all such substances should be guarded against.

Vaccines are the most valuable nonspecific measures. Rackemann's<sup>19</sup> tenets for vaccine therapy: "no reactions, no results," whether one uses autogenous or stock vaccines, still hold good. In our hands tuberculin has not proved advantageous over other types of vaccine. A good stock catarrhal vaccine will usually serve the purpose. In administering vaccines it is well to start with a small dose of 0.25 cc. and increase it by 0.1 cc. at four to seven-day intervals. One always aims to obtain a local reaction the size of a silver dollar. Occasionally we see a patient who is sensitive to bacterial proteins and whose asthma becomes aggravated within two to twelve hours after the injection of vaccine. In such instances the vaccine should be diluted with saline 1:100 and treatment instituted with 0.1 cc. of this dilution. At all times should the dose be kept below its injurious level. Reports in the literature on the particular advantages of autogenous vaccines are not lacking (Thomas-Asthma),<sup>20</sup> but in many trials we have never been able to substantiate such claims and an extensive experience shows results with stock vaccines quite the same as those with autogenous.

**Oral Desensitization.**—When a sensitivity to the ingestion of certain foods is responsible for hay fever or asthma, desensitization by the subcutaneous method is ineffective. Here oral desensitization may be tried. The technic of oral desensitization is as follows: 1 drop of the offending food (egg white or milk) is diluted in 1 quart of water and a teaspoon of the mixture is taken three times a day, after meals. If no ill effects follow, the same amount of food is diluted in a pint of water and again three teaspoons taken a day. The quantity of diluent is gradually decreased from day to day

until it consists of only one ounce of water. From then on the quantity of food is increased instead of diminishing the amount of diluent. Thus we add 2, 3, 4, 5 drops of the food to the ounce of water until the patient is able to take the whole food with impunity. Theoretically this method works out better than practically, but at the same time it is worthy of trial. Nonspecific oral desensitization as had been advocated by Urbach,<sup>21, 22</sup> at first with heterogenous and later on with homologous propeptons have not created sufficient enthusiasm in this country to deserve unreserved recommendation.

#### OTHER METHODS OF TREATMENT

Satisfactory results in the treatment of hay fever and asthma with viosterol in high concentration (10,000 units) have been reported by Rappaport<sup>23</sup> *et al.* Commencing about ten days before the expected date of pollination, 4 to 10 drops of the drug are administered daily. Where tolerance permits, the dose may be increased up to 60 minims a day. When treatment with viosterol was combined with specific desensitization the end-results were more satisfactory. The treatment of asthma with hormones of the adrenal cortex and sodium chloride as recently proposed by Pottenger,<sup>24</sup> *et al.*, offers a direct approach to the host on the basis of a hormone deficiency. We shall be hopefully awaiting further developments of this method. Beckman<sup>25</sup> reports his results on the treatment of hay fever with large doses of hydrochloric acid and finds them comparable to the results obtained from treatment by desensitization. Our own experiences with this method of treatment are scant. The use of nose and mouth masks is often indicated in the occupational allergies, such as in bakers who are sensitive to flour and who fail to obtain palliation through specific desensitization. Such masks, though cumbersome and conspicuous looking, enable the patient to gain some comfort at his work. Air conditioning<sup>26</sup> in pollen disease is helpful, at least as long as the patient remains in the air-filtered room. Upon leaving the room, however, the symptoms recur. Hence, air conditioning should be used only as an adjunct to, but not as a substitute for, specific desensitization.

Nasal ionization for the treatment of vasomotor rhinitis as proposed by Warwick,<sup>27</sup> has received considerable attention of late. This method is still new and though apparently productive of immediate relief in about 50 per cent of the cases, its possible injurious effect on the nasal mucosa<sup>28</sup> calls for rational conservatism.

### SUMMARY

In retrospect, the question may arise as to what constitutes the recent advances in the treatment of hay fever and asthma? Since Noon and Freman's introduction of specific therapy in pollen disease and the subsequent application of this method to other forms of vasomotor rhinitis and of asthma, there has been but little progress on this subject. Emphasis, however, has been noted throughout the literature on the fundamentals of allergy and on its chemical and immunologic phases. Only through such broader concepts of the subject is an approach to rational therapy possible. These tendencies are witnessed in Rackemann's<sup>20</sup> recent review on the progress of allergy: out of 372 publications he selected 111 as representative of the best thoughts on the subject. Of these 111 only 4 are given to "treatment," while the others deal with the various phases of allergy at large. And yet, clinical experience tends to crystallize the adaptation of current therapeutic measures and these we have attempted to stress in this communication. One other fact is worthy of comment. The allergic concept of asthma and hay fever has sent into oblivion some of the older measures of which physicians, in the preallergic era, availed themselves. Amongst these, balneotherapy, physiotherapy, hydrotherapy, general tonic measures, were most noteworthy. So thoroughly have all these been forgotten, that their consideration anew might justly be included in the "Recent Advances." But the subject is vast and would in itself form an important communication.

### APPENDIX I

A suggestive list of foods and inhalants for use in routine skin-testing of patients. This list should be supplemented by such other proteins as may be indicated from the history of the case.



*Foods:*

<i>Cereals.</i>	<i>Meats.</i>	<i>Fish.</i>	<i>Shell-fish.</i>	<i>Vegetables.</i>
wheat	beef	haddock	crab	potato
rye	veal	halibut	lobster	tomato
barley	lamb	salmon	oyster	asparagus
corn	chicken	cod	shrimp	beet
oats	pork	mackerel	clam	cabbage
rice		flounder	scallop	onion
				carrot
<i>Fruits.</i>	<i>Miscellaneous.</i>	<i>Nuts.</i>	<i>Egg and milk.</i>	
apple	cinnamon	almond	egg white	kidney bean
pineapple	poppyseed	walnut	egg yolk	lima bean
banana	nutmeg	cocoanut	milk (cow)	lettuce
pear	mustard		lactalbumin	mushroom
peach	ginger			sweet potato
plum	buckwheat			
orange				
grapefruit				
grape				
olive				
cheery				
strawberry				

*Dusts:*

<i>Epidermals.</i>	<i>Miscellaneous.</i>
cat hair	kapok
dog hair	cottonseed
cattle hair	house dust
horse dander	flaxseed
hog hair	orris root
feathers	pyrethrum
chicken	boxwood
duck	
goose	
goat hair	
sheep wool	

*Pollens:* These vary with different localities. Hence it is essential to establish a familiarity with the important pollen flora, of a given area before undertaking pollen tests. Mr. Durham of the Abbott Laboratories has always been cooperative in rendering such information.

## APPENDIX II

## ROWE'S "ELIMINATION DIETS"

	<i>Diet No. 1.</i>	<i>Diet No. 2.</i>	<i>Diet No. 3.</i>
Cereal.....	rice	corn tapioca	rice rye
Bread.....	rice biscuit	corn pone	rye-rye
Meat or Fish.....	lamb	bacon chicken	beef
Vegetables.....	lettuce spinach carrots	squash asparagus peas artichokes	tomatoes beets string beans
Fruits and jams and fruit drinks.....	lemons pears peaches	pineapple apricot prunes sugar	grapefruit pears peaches sugar

Miscellaneous.....	sugar	Mazola oil	Wesson oil
	olive oil	salt	salt
	salt	Karo corn syrup	gelatin
	gelatin		syrup made from cane
	syrup		sugar flavored with
	made		maple.
	from cane		
	sugar		
	flavored		
	with		
	maple.		
	olives (unstuffed)		

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oats	pork	mackerel	clam	cabbage
rice		flounder	scallop	onion
<i>Fruits.</i>	<i>Miscellaneous.</i>	<i>Nuts.</i>	<i>Egg and milk.</i>	
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pineapple	poppyseed	walnut	egg yolk	lima bean
banana	nutmeg	cocoanut	milk (cow)	lettuce
pear	mustard		lactalbumin	mushroom
peach	ginger			sweet potato
plum	buckwheat			
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		tapioca	rye
Bread.....	rice biscuit	corn pone	rye-rice
Meat or Fish.....	lamb	bacon	beef
		chicken	
Vegetables.....	lettuce	squash	tomatoes
	spinach	asparagus	beets
	carrots	peas	string beans
		artichokes	
Fruits and jams and fruit drinks.....	lemons	pineapple	grapefruit
	pears	apricot	pears
	peaches	prunes	peaches
		sugar	sugar

Miscellaneous.....	sugar olive oil salt gelatin syrup	Mazola oil salt Karo corn syrup	Wesson oil salt gelatin syrup made from cane sugar flavored with maple.
	made from cane sugar flav- ored with maple. olives (unstuffed)		

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## CLINIC OF DR. EDWARD S. EMERY, JR.

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### RECENT ADVANCES IN DIETOTHERAPY

I WANT to present three cases to illustrate the importance which food has come to play in the study and practice of medicine.

**Case I.**—The first patient is an American schoolboy of fourteen who entered the hospital because of marked weakness and pain in the legs. The family and past history are negative. He lives in unhygienic surroundings and has been a peculiar eater, largely by choice. He has not been eating any fruit and an almost negligible quantity of vegetables. He began to have trouble with pain in his feet last June. He attributes this to fallen arches. He noticed "hard swelling" in the muscles both below and above the knees. Six weeks ago he developed marked weakness, and for the last four weeks it has been impossible for him to walk across the street. For the last few weeks he has had to go about on crutches. He has had sore gums which bleed on brushing the teeth.

Physical examination shows marked pallor of the skin. He is poorly developed. The gums are red. The alveolar tissue is spongy and hypertrophic and ulcerated at the edges. The molars are loose. There is marked tenderness over the epiphyses of the femur and tibia of both lower extremities.

The urine is negative, the hemoglobin is 95 per cent, the red count is 4,530,000, and the white count is 10,500. The blood smear is normal and the platelet count is 335,000.

His only treatment has been an addition to the hospital diet of 200 cc. of orange juice three times a day, which he has received for four weeks. His symptoms and signs have disappeared entirely on this régime. This patient was suffering from scurvy, one of the diseases known to be the result of a vitamin deficiency.

Eijkman's observation in 1897 that fowls acquired polyneuritis on a diet of polished rice gave a new approach to the study of disease. With Funk's contribution in 1910 that beriberi is the result of a deficiency in what he termed a vitamin, the way was cleared for the great progress that has been made in our studies on nutrition. But as so often happens, following new discoveries, our enthusiasm tends to lead us into therapy which our present knowledge does not justify.

It is, therefore, wise to consider how much we know about dietetic therapy.

We have learned much about the vitamins in recent years. We know that the absence of a vitamin can produce severe diseases which clear up almost miraculously with the introduction of the necessary foodstuff.

The disease known as xerophthalmia responds to the administration of vitamin A, beriberi to vitamin B, scurvy to vitamin C and rickets to vitamin D. Also we have learned much about the nature of these vitamins. Vitamin B has been crystallized and has the chemical form of a hydrochloride of picrolonic acid. C is known to be 1-cevitamic acid and D is a sterol. Hence, these substances are chemical compounds which we believe may act as catalysts; that is, they aid or hasten what otherwise may be an ineffective chemical reaction. Vitamin B seems to influence the oxidation of carbohydrates. Vitamin C has been shown to be a strong reducing agent in the test tube. Vitamin D influences the action of calcium and phosphates in the bones although it is not yet known in what way it does this.

We have also learned much about how the vitamins affect the body and its different systems. Vitamin A influences the epithelial tissues of the body and in its absence the skin tends to become cornified. A reduction of tone and motility of the gastro-intestinal tract and a polyneuritis follows a deficiency in vitamin B. An absence of vitamin C results in a lack of an intercellular cementing substance with a resulting leakage or extravasation of blood into the tissues. Vitamin D aids the absorption of calcium from the intestinal tract and seems to influence the chemistry of calcium and phosphorus within the body.

In addition to these facts, which are now generally accepted, there has been a large amount of information reported from laboratory studies which cannot be dealt with completely at this time and some of which is in dispute. Some workers report that vitamin A specifically stimulates the intestinal mucous membrane and directly or indirectly the formation of blood platelets. An atrophy of the intestinal villi is said to occur in the absence of this vitamin. A lack of vitamin B is said to result in congestion and hemorrhage into the bone

marrow. Also it is said to produce an atrophy of lymphoid tissue with a lymphopenia characteristic of nutritional changes.

Interesting as these findings may be, the clinician must remember that they are still in the phase of investigation. If, for example, a lack of vitamin B produces atrophy of lymphoid tissue and a lymphopenia, it does not follow that the finding of a lymphopenia should necessarily be treated with vitamins.

The question of how far we should go in using vitamins is hard to evaluate at the present time. Some very good men have advanced the idea that many symptoms may be the result of an insufficient amount of these substances. However, we must not forget that a very small amount of a vitamin is required to eradicate completely all vestiges of those conditions like scurvy, which are known to be caused by an inadequate intake of a vitamin. Therefore, one should be cautious about attributing other conditions, frequently with indefinite symptoms, to an insufficiency of vitamins, particularly if the patients seem to be taking a normal diet. Certainly it is true, that in this period when the population is "vitamin conscious" very few persons take an insufficient quantity. The diet of most adult Americans contains enough vitamins to prevent the picture of a severe insufficiency such as occurs in beriberi and scurvy. The present free use of vitamin mixtures either with or without a doctor's sanction would seem to preclude an insufficient intake in most patients.

Therefore, if indefinite complaints of bodily aches, chronic indigestion, lack of vitality, etc., depend upon a vitamin lack, it is reasonable to believe that in some cases the difficulty may be an inability of the body to utilize the vitamin rather than an inadequate supply.

The second patient illustrates another group of diseases which can be relieved by diet.

**Case II.**—This thirty-six-year-old married clerk entered the hospital because of persistent weakness and fatigue of two years' duration. The family and past history are irrelevant. She felt perfectly well until twenty-two months before admission when she caught cold and suffered from headache, malaise, anorexia, weakness and fever. She remained in bed for four and a half months after which she began a slow convalescence which was marked by fatigue, dyspnea, palpitation and weakness. By fall she was able to work half a day but with great effort. Two months ago she was attacked suddenly by what she described as an "awful dead, all gone feeling." Her physician said



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she was anemic and advised rest. About three months before entry she began to be troubled with nausea, vomiting and gagging after eating.

Physical examination revealed an emaciated woman with a lemon yellow tint to the skin. The face was drawn. The sclerae were very white. Many flame-shaped hemorrhages were present in both fundi. At the time of entry her hemoglobin was only 15 per cent, red blood count 880,000 and white blood count 3800. The red cells showed marked achromia, anisocytosis, poikilocytosis, normoblasts, polychromatophilia and stippling. No platelets were seen. Following one transfusion and intramuscular injections of liver extract she began to improve. After one month the hemoglobin was 86 per cent, the red blood count was 5,480,000 and the white blood count was 8500. Now she feels perfectly well.

This patient suffers from pernicious anemia, a disease which presents, or at any rate emphasizes, certain problems which scurvy does not. Scurvy develops in a normal person from an inadequate supply of vitamin C, whereas pernicious anemia may occur on a normal diet with an inadequate gastric function. The patient with pernicious anemia develops symptoms because of an inability to manufacture from a normal diet something essential to the body. Therefore, the clinician must remember that there are at least two factors in the study and treatment of deficiency diseases. One is the amount of essential substances available in the diet. The other is the ability of the body to utilize these substances.

With our present limited knowledge of the subject, it is alluring but dangerous to speculate on how many of our medical problems are associated with a deficient state. Pellagra and sprue are two clinical entities which seem closely allied to pernicious anemia. Both are benefited by dietetic treatment. Brewer's yeast and fresh liver are said to be especially rich in the pellagra-preventive substances. Sprue is reported to be relieved by liver extract. Although the three diseases have certain qualities in common they present a sufficiently characteristic picture to make possible a clinical differentiation. We have yet to learn what causes these various pictures. Are they the result of a difference in the utilization of the same foodstuffs, and if so, upon what does the difference in utilization depend? As an evidence of how little we know about this problem is the fact that as late as 1934 one of the standard textbooks retained sprue under the infectious diseases. Our lack of knowledge about this group of diseases emphasizes that we should not expect to cure all patients that

suggest a deficiency by the simple means of giving a normal diet.

Finally, I want to present very briefly this last case for your consideration because it involves the mineral content of the food.

**Case III.**—This young boy of ten years was brought into the outdoor department following an automobile accident. He was not hurt seriously, but an x-ray was taken of his leg for a possible fracture. The film revealed a healed rickets. The patient is now well but is of interest because he shows evidence of a former illness which was produced by a diet inadequate in vitamin D, phosphorus, or both. The case is an example of the importance which diet plays in providing the body with sufficient minerals.

Our knowledge about the effect of minerals on the body has increased rapidly of late. We have learned that certain minerals are essential to the normal functioning of tissues, as for example, iodine in relation to the thyroid, iron to the blood, calcium and phosphorus for the bones.

The salts maintain the reaction of the blood and control the osmotic pressure in the organism. An imbalance in the amount of the various minerals and salts results in widespread systemic effects. Alkalosis is met with not uncommonly from continued loss of chlorides through vomiting and the alkaline treatment of peptic ulcer. Many of the symptoms of heat exhaustion have been traced to an excessive loss of sodium chloride in the sweat.

Our recent knowledge has supplied us with therapeutic triumphs. The treatment of heat exhaustion with sodium chloride is of distinct value. The great contribution to our therapy in lead poisoning came from Aub's study of the behavior of minerals within the body.

More recently it has been reported that an acid base diet is useful in treating patients with renal calculi of a certain type.

We can look forward to further advances in therapy. Further knowledge of the chemical behavior of minerals within the body should open the way for a more efficient treatment of edema. But such advances can only come through the information obtained from careful laboratory studies. Meanwhile the profession must guard against foolish therapy based on inadequate knowledge. It is worth emphasizing that the

amount of minerals which the body requires is small. The normal adult needs roughly 0.015 Gm. of iron, 1.32 Gm. of phosphorus and 0.68 Gm. of calcium per day. Therefore, the actual needs of the body are easily supplied. The profession is facing the same problem that has so often presented itself with any new knowledge. The public will become "mineral conscious," and we can look forward to a wave of injudicious treatment.

Only the discriminating use of our new knowledge by the profession can serve as a brake against foolish therapy and quackeries which always arise at such a time.

## CONTRIBUTION BY DR. FREDERICK T. LORD

BOSTON

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### CERTAIN ASPECTS OF THE COMMON COLD

LITTLE is known regarding environmental factors as a cause of colds. The hypothesis is presented by Kerr and Lagen<sup>1</sup> that the disease represents a failure of the body to adjust itself to a varying environment, as against an infectious origin. In support of this theory, presumably susceptible subjects under conditions arranged for maximum comfort, failed to develop colds under intimate exposure to individuals in the early stages of the disease or after inoculation with nasal secretion from persons with colds.

The greatly increased incidence of colds during the colder months of the year lends support to atmospheric conditions as a factor. Van Loghem<sup>2</sup> noted that epidemics of colds in Holland follow sharp drops in temperature. Milam and Smillie<sup>3</sup> also found that outbreaks of colds in the tropics coincided with sudden fall in temperature of a few degrees. Paul<sup>4</sup> states that epidemics of colds occurred on the research vessel Carnegie after many days or weeks out of port after the ship entered a cold current from warmer waters.

The investigations of Rossbach,<sup>5</sup> Müller,<sup>6</sup> Miller and Noble<sup>7</sup> and Mudd, Grant and Goldman<sup>8</sup> suggest that chilling of the body surface in animals and man may induce changes favorable to local invasion of the mucous membranes by organisms already present and otherwise harmless.

<sup>1</sup> Tr. Assoc. Amer. Phys., 49: 245, 1934.

<sup>2</sup> Jour. Hyg., 28: 33, 1928-29.

<sup>3</sup> Jour. Exp. Med., 53: 733, March, 1931.

<sup>4</sup> Paul and Freese: Amer. Jour. Hyg., 17: 517, May, 1933.

<sup>5</sup> Berl. klin. Woch., 1882.

<sup>6</sup> Deutsche klinik, 1903-04.

<sup>7</sup> Jour. Exp. Med., 24: 223, 1916.

<sup>8</sup> Ann. Otol., Rhinol. and Laryngol., March, 1921.

In spite of such observations, there is nothing to support the belief that environmental factors alone are of importance. The great frequency of exposure in wet weather, wet feet, sitting in wet clothes or draughts and rapid cooling when overheated without ill effects is suggestive of little more than a chance relation. It is difficult to estimate the importance of lowered temperature, in view of the tendency in cold weather to live in crowded and poorly ventilated rooms with consequent greater opportunity for spread by contact.

Nansen's often quoted experience of freedom from colds among members of his expedition under exposure to the rigorous climate of the far North is against exposure to cold as a factor. The development of colds and coughs among many of his party when, on their return, they landed at a thickly settled port, is strikingly suggestive of a contagious origin.

The investigation of small isolated communities has apparently established spread of the disease by transmission from person to person. Studies in certain Eskimo settlements (Greenland) by Heinbecker and Irvine-Jones<sup>9</sup> and in Longyear City (Spitzbergen) by Paul and Freese<sup>10</sup> indicate that outbreaks of colds arise from exposure to persons from without and involve a large proportion of the population. Paul and Freese find in a group of 500 persons in Longyear City that colds are largely concentrated into an explosive epidemic following the annual resumption of steamer traffic with Norway. They suggest that the population is too small to permit transfer of the inciting agent from person to person with sufficient frequency to retain its original virulence and give rise to an epidemic during the months of isolation from the outside world.

A filtrable virus was suggested as the cause of colds by the investigations of Kruse<sup>11</sup> and Foster.<sup>12</sup> Dochez and his associates have made additional contributions of great value. They find that anthropoid apes and especially chimpanzees are susceptible and that infection is readily communicated from man to the ape and from one ape to another. The dis-

<sup>9</sup> Jour. Immunol., 15: 395, 1928.

<sup>10</sup> Amer. Jour. Hyg., 17: 517, May, 1933.

<sup>11</sup> Münch. Med. Wchnschr., 61: 1547, 1914.

<sup>12</sup> Jour. Amer. Med. Assoc., 66: 1180, April 15, 1916.

ease can be produced in an experimental subject by inoculation with filtered nasal secretion from an individual with a cold, the organism recovered by culture and the disease reproduced by inoculation with the culture material. The inciting agent remains active after many generations of growth in tissue cultures. Production of colds with bacteria-free filtrates excludes the presence of ordinary organisms as a cause. The constituents of the culture material itself and the heated culture of the virus at times produced temporary irritation, but not the manifestations of colds. An origin of colds from infection with a filtrable virus must be regarded as established.

As with other infectious diseases, not all persons appear to be susceptible. Following a cold there is a short period of immunity, the duration of which may be estimated from the observations of Paul and Freese at a minimum of twenty-three days and an average of seven weeks. Dochez's experiments on chimpanzees indicate that resistance to reinfection lasts only about a month. A short period of immunity increases the difficulty of solving the problem of prevention by any method of artificial vaccination.

Investigation of the flora of the nasopharynx under normal conditions and during colds by Dochez and his associates, Burky and Smillie,<sup>13</sup> Kneeland,<sup>14</sup> Milam and Smillie<sup>15</sup> and Paul and Freese<sup>16</sup> suggests that the bacteria harbored in the upper air passages are not to be regarded as the inciting agents of the disease. They play an important part, however, as secondary invaders. The seriousness of a cold is almost entirely due to its tendency to initiate such disturbances of a grave nature as bronchitis, otitis media, sinusitis, bronchopneumonia and lobar pneumonia. Among patients with lobar pneumonia, for example, 76 per cent give a history of a cold within a short period of the onset of pneumonia. Smillie and Caldwell<sup>17</sup> found pneumococci increased in the nasopharynx or persons with acute colds, and Dochez, Mills and Kneeland<sup>18</sup>

<sup>13</sup> Jour. Exp. Med., 50: 643, 1929.

<sup>14</sup> Ibid., 51: 617, 1930.

<sup>15</sup> Ibid., 53: 733, 1931.

<sup>16</sup> Loc. cit.

<sup>17</sup> Jour. Exp. Med., 50: 233, Aug., 1929.

<sup>18</sup> Proc. Soc. Exp. Biol. and Med., 30: 314, Dec., 1932.



noted in chimpanzees during the early stages of the cold, whether spontaneous or experimental, a great increase in the numbers and the area of distribution of the common pathogens of the upper air passages, such as the influenza bacillus, pneumococcus and hemolytic streptococcus. Under the influence of infection of the animals with the virus of the common cold, a transformation was observed from the S to the R type of influenza bacillus during the period of the cold, while only R forms could be cultivated during the intervening period. Such observations suggest that one of the most important effects of the virus of the cold is to incite activity on the part of potentially pathogenic micro-organisms present in the nasopharynx at the time of infection.

There is no practical method for the prevention of colds under ordinary conditions of life and none of the numerous measures suggested has been proved to be successful. The difficulty of avoiding contagion is suggested by the observation of Heinbecker and Irvine-Jones<sup>19</sup> that it was not necessary for members of the expedition to have a respiratory infection for the disease to appear among the natives. It is, nevertheless, desirable to attempt to prevent colds in infants, invalids and the aged by the avoidance of known contact and in them special care should be exercised against exposure to rapid changes of temperature. Adequate ventilation, maintenance of an equable temperature within doors and humidification may prevent the development of complications in those who have colds.

On the part of those with colds, for the protection of others, precautions should be taken to prevent droplet and contact infection. It is possible that transfer of bacteria heightened in virulence by the inciting agent of the cold may more readily give rise to infection on transfer to others.

There is no evidence that hardening or toning-up processes, ultraviolet radiation, vitamins or nasal douches are useful in prevention. Vaccination with a mixed vaccine containing killed bacteria ordinarily found in the nasopharynx has not, on the whole, proved successful in diminishing the incidence of colds when large controlled series have been investigated.

Inoculation with a composite vaccine has been proposed

<sup>19</sup> *Loc. cit.*

for the purpose of diminishing the frequency and severity of the complications of colds. Kneeland<sup>20</sup> compares the results in 23 infants given a course of 9 and later of 7 inoculations, with an equal number of controls. There was no difference in the incidence of minor respiratory infections of the type of the common cold in the two groups. The severity of the subsequent respiratory disease measured by the duration of fever, however, was diminished and there were 2 cases of pneumonia in the vaccinated against 5 in the controls. Further carefully controlled experiments of a similar nature are desirable before a favorable effect can be regarded as established.

Colds are self-limited. There is no specific treatment. Symptoms may be relieved and it is possible that complications may be averted by observance of certain precautions. In all cases, while there is fever, rest in bed is desirable. Irrespective of fever, in the more severe types and in infants and the aged or infirm, rest in bed is also advisable. During the disease and also while cough and expectoration persist, caution should be exercised against fatigue, chilling of the body, exposure to draughts without sufficient clothing and rapid cooling when overheated. An abundant intake of fluid is to be recommended and a mild laxative, if necessary, for constipation.

Headache and general discomfort may be alleviated by acetyl-salicylic acid (aspirin), 5 grains, repeated if necessary, every four to six hours for 4 to 6 doses, or such coal-tar products as phenacetine, 3 grains, with caffeine, 1 grain, repeated if necessary, every three hours for 3 or 4 doses may be used if these symptoms are sufficiently troublesome. It is undesirable to use amidopyrine or drugs in combination with it, in view of its probable implication as a cause of agranulocytosis in susceptible individuals. If the headache and general pains are especially distressing, Dover's powder, 10 grains, may be ordered. In the investigations of Diehl<sup>21</sup> the highest percentage of good results followed the use of a combination of codeine and papaverine; *i. e.*, "co-pavin," containing codeine sulphate  $\frac{1}{4}$  grain and papaverine hydrochloride  $\frac{1}{4}$

<sup>20</sup> Jour. Exp. Med., 60: 655, 1934.

<sup>21</sup> New York State Jour. Med., 35: 109, Feb. 1, 1935.

grain. Toxic symptoms occurred in 4.9 per cent of the cases. In his experience, this preparation as well as certain other opium derivatives were followed by prompt diminution and complete relief of nasal discharge and congestion. The routine use of opium or its derivatives does not seem justifiable, but may be desirable in unusually severe cases. The local application of 1 per cent ephedrine sulphate dropped in the nose produced temporary relief of nasal congestion, but the progress of the cold was apparently unaffected. Toxic symptoms were observed in 4.3 per cent.

## CLINIC OF DR. WILLIAM H. ROBEY

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#### THE SIGNIFICANCE AND INTERPRETATION OF HEART MURMURS IN GENERAL PRACTICE

If you are surprised that one takes the time to discuss this subject when so much study is being given to the problems of cardiac muscle efficiency, let me remind you that the cardiac murmur is still a puzzle to many general practitioners. In my student days no cardiac sign was given as much thought as the murmur, and its discovery often meant a diagnosis of organic heart disease, even when the patient was apparently in perfect health, since it was impossible for the doctor to believe that a heart could emit such a sound unless diseased. As a result, a diagnosis of cardiac disease was made and the patient's life restricted; with the further result, in some cases, of transforming a healthy person into a hypochondriac. For several years I gave a course to graduate students, principally those who had been undergraduates during the days when the cardiac murmur was considered to be of such great importance. Upon being asked to examine a heart, the student immediately placed a stethoscope over the valve areas and his opinion was formed by the presence or absence of a murmur. Before the end of the course the students were trained to evaluate the medical history and many cardiac and circulatory signs before using the stethoscope. Undergraduates were also taught to diagnose well-marked cases of mitral stenosis by palpation of the precordium and the radial pulse before listening to the heart. The idea was to instill in the mind of the student the necessity of merely adding a murmur to the other physical signs rather than allowing the murmur to become the dominant factor in cardiac diagnoses. The physician must constantly remember

that serious heart disease, such as syphilitic aortitis, hypertensive heart disease and coronary disease, may exist without any murmurs. I once saw a forty-seven-year-old man, apparently in the pink of condition, who had no cardiac nor circulatory defect which could be discovered, but who had repeated attacks of most severe nocturnal angina pectoris, one of which terminated in sudden death. Again, some conditions, while slight, may give rise to loud murmurs which disappear with a serious advance of the disease. In hypertensive heart disease a sudden drop in pressure and the disappearance of a mitral systolic murmur are often ominous signs of cardiac muscle failure. In mitral stenosis the presystolic diastolic murmur generally disappears with the onset of auricular fibrillation, although not always.

The mechanical causes of murmurs, such as changes in viscosity of the blood or stretching of the valve rings, have been discussed for years and need not concern us now. The important points to remember are the following:

Murmurs are caused by the vibration of the valve cusps and walls of the heart and of the great vessels when the blood flows from a passage of narrowed caliber to one of much greater caliber, or by the vibration of some tissue attached to a valve, to the heart wall, or to a vessel wall, with the other end free to move in the blood stream. Speed and strength of the blood flow are the factors which intensify or diminish the sound of murmurs. If the flow is strong the murmur will be loud, if of decreased strength the murmur will be faint, while it may disappear completely if the flow loses power to a marked degree. In mitral stenosis, for example, when the left auricle is well compensated and the valve is somewhat distorted, a rough, vibratory presystolic type of diastolic murmur is heard, but when the auricle goes into fibrillation the speed is increased but the strength of flow is reduced so that the murmur subsides or varies in degree of intensity, or it even may cease to exist.

Another cause of murmurs is edema of the cardiac structures which occurs in some of the acute infections, especially rheumatic fever. Such murmurs must be classed during the illness as functional and not as organic until their character and permanence can be determined. Therefore, when mur-

murs are heard during an acute illness, the attending physician should not give a hasty opinion as to their significance.

Murmurs, like other heart sounds, may be louder in thin persons and fainter in the obese or muscular. Emphysema may diminish the intensity by pushing the heart away from the chest wall. Fluid accumulating within the pericardial sac, especially when evenly or anteriorly placed, will render less clear all heart sounds.

### THE SYSTOLIC MURMUR

As has already been said, the systolic murmur has been the cause of much perplexity in the minds of examiners. During the World War it was, of necessity, given considerable attention; doubtless many healthy young men were declined for service merely because of a sound which suggested a systolic murmur. Some, however, were enlisted and the regimental surgeon sent them to the base hospital with the question of discharge. The consultant's duty was to decide whether the murmur was organic or functional—whether or not it was indicative of some organic lesion which would declare itself under the stress of action. We went into the medical history with great care and looked for further signs. If the findings were otherwise negative we made a diagnosis of functional murmur and signed the soldier for full duty. Similarly Sir Thomas Lewis returned thousands to the front who proved able to carry on successfully. Some have even gone to the point of saying that the mitral systolic murmur is of no importance, and that it may be disregarded in the young unless there are indications of mitral stenosis. Indeed, this might be so, were it not for the fact that the first murmur of mitral stenosis is sometimes the mitral systolic murmur. And the opinion that valvular findings are unimportant would also be true, since the myocardial condition is the one which determines the efficiency of the circulation, were it not that the state of the valves, especially in the young, regulates in a measure, the amount of work which may safely be thrown upon various parts of the heart muscle.

When I read some descriptions of the differentiation between functional and organic systolic murmurs, I am reminded

of one of our professors whom I, as a student, asked when a case of appendicitis should be operated upon. He replied, "Show me the case." Laënnec in 1819 described sounds in the heart which he considered were always caused by valvular lesions, but later he denied them any value because the post-mortem examination often failed to show the lesion which had been foretold by the murmur. This failure to discriminate between functional and organic murmurs continued for years, notwithstanding our great advance in the interpretation of cardiac and circulatory signs; even today some confusion on this point continues to exist.

The two chief findings in the determination of a systolic murmur are duration and intensity, and of these, the former is the more important. To make a definite diagnosis of a systolic murmur the bruit must have an appreciable duration after the first sound, and continue into systole. Do not mistake a slight prolongation of the first sound for a murmur.

Short, faint systolic murmurs are considered functional and of little importance, while prolonged intense ones are thought to be organic. Levine<sup>1</sup> grades mitral systolic murmurs by their intensity, which he divides into six degrees, beginning with the first, which is very faint and which he says few general practitioners hear, and ending with the sixth, which is rare, but so intense that it can sometimes be heard when merely standing in front of the patient (in my own experience I remember but one such extreme case) and physicians working with him in the clinic were able in most instances to estimate the degree of intensity of a murmur and were usually in entire agreement. This is a very interesting method for a group under expert leadership, but for those who must work alone and whose training may not have been specialized, it offers comparatively little that is of practical advantage.

Intensity is important, but differing conditions in patients suffering from the same lesion may cause it to vary—this refers to emphysema, thick chest wall, and the degree of cardiac muscle strength. Duration can be more easily determined following the rules already given.

While systolic murmurs are said to occur rarely in normal individuals, many are heard without other evidence of cardiac

<sup>1</sup> Jour. Amer. Med. Assoc., 101: 436-438, Aug. 5, 1933.

disease. When one is heard we immediately attempt to decide whether it represents organic valvular disease or is merely a functional murmur. Regurgitation of blood through the mitral valve produces a systolic murmur over the area of cardiac impulse, but regurgitation of blood and its systolic murmur do not necessarily indicate disease of the mitral valve. When the New England Heart Association in 1926 made a survey of the 119,337 school children of Boston, 2311 who, because of murmurs, were suspected by the school physicians of some type of heart disease, were examined and separated into groups. The majority, 1344, could be safely reassured they had no significant disease. The doubtful group, 265, required reexamination until the diagnosis could be settled. The potential heart disease group needed to have the importance of their condition brought home to them. The most important discovery was the small number of children having organic disease—only 160 were in hospitals, and these, added to the ambulatory cases, totaled 785, or the surprisingly low percentage of 0.66 of discovered cases. In one room where there were 52 young children, every one had what the school physicians called a systolic murmur, and yet the medical history, physical well-being, activity and absence of other cardiac abnormalities made us pass the hearts as normal.

Conditions which dilate the left ventricle may enlarge the valve opening so that perfectly normal valve cusps may not be able to approximate and will therefore fail to prevent a reflux of blood from ventricle to auricle during the contraction of the former chamber. On the other hand, the chambers of the heart and the mitral ring may be normal, yet the cusps are retracted, the valve is incompetent and a murmur occurs during ventricular systole.

A mitral systolic murmur in a young person, especially if it has the proper duration and some degree of intensity, should be looked upon as evidence of organic valvular disease until we can satisfy ourselves that it is functional, while a similar murmur in an elderly person is very apt to be functional and not caused by any pathological changes in the valve itself, but is a result of cardiac muscle pathology. In fact, many serious cardiac disturbances in the elderly occur without any murmur. In the young it is far more important,



meaning, as it does, when we have proved it to be organic, a pathological condition of the valve which gradually throws more work upon adjacent chambers and eventually causes an inefficient heart.

How are we to determine whether a mitral systolic murmur is functional or organic? First of all, there is the medical history. Has the patient ever had rheumatic fever or its allies? We must remember that rheumatic fever in a child frequently has quite a different train of symptoms from that in an adult; he may have a sore throat, vague pains in the muscles, fever, nervousness and irritability; or there may be repeated attacks of sore throat without other symptoms which the patient or his family are able to recall, but the hot, red, painful joints of the adult are often not in evidence. The diagnosis of rheumatic heart disease is almost certain, even if the other signs of mitral stenosis cannot be demonstrated, provided one finds that the murmur has duration and a certain degree of intensity combined with a history of rheumatic fever.

A seventeen-year-old girl was brought to my office with a history of always being delicate. During the summer she had lost 12 pounds, although she was on a farm. She gave a history of rather frequent colds but no rheumatic fever, sore throats nor tonsillitis. Occasionally there was nose-bleed. She had a good appetite and slept well; her chief complaint was very easy fatigue. If she went out for an evening she would be tired the following day. She was thin and of poor color. The blood pressure was 130-90. The heart was normal to percussion and fluoroscope with a loud, blowing systolic murmur heard over the entire precordia and in the back. The impulse was heaving and the cardiac rate 120. There was no arrhythmia, no diastolic nor presystolic murmur, no thyroid enlargement, no cardiac thrill, no tremor of hands, no incoordination. The lungs and abdomen were negative. There was no edema. The hands were cold and slightly cyanotic. In the differential diagnosis, I considered first mitral stenosis and then effort syndrome and hyperthyroidism. In view of the fatigue, occasional nosebleeds and marked systolic murmur, the mitral stenosis seemed most probable. She was given a régime of rest and quiet with instructions to report in two weeks, but six days after I saw her, her mother stated that her daughter had a paralysis of the left arm and leg. This clarified the diagnosis of mitral stenosis. Two months later I saw her in consultation with her physician and found, in addition to the hemiplegia, a systolic murmur, diastolic and presystolic murmurs and a marked apical thrill. The pulse was small and 140 in rate.

Another girl entered the hospital many years ago with a systolic apical murmur of moderate intensity without any murmurs during diastole. There was no history of rheumatic fever but there had been occasional attacks of nosebleed. She was discharged with a diagnosis of mitral regurgitation but

returned in about two weeks with a diastolic murmur in addition to her systolic one and a certain amount of arrhythmia. This made the diagnosis of mitral stenosis quite apparent.

If we can satisfy ourselves that there is some cardiac enlargement with a persistent mitral systolic murmur it can be assumed that there is organic valvular disease. Similar findings in a middle-aged person who is developing easy fatigue, breathlessness on exertion or during sleep, or some type of arrhythmia doubtless would indicate organic cardiac disease but the murmur is merely relative. During the course of rheumatic fever, the physician should reserve his opinion about any murmurs he may hear until the fever has entirely subsided and the patient's convalescence has been well established.

A fourteen-year-old girl was on our service at the Boston City Hospital with a violent and prolonged attack of rheumatic fever, and during the height of the disease she developed a well-marked presystolic murmur. There was a temptation to make a diagnosis of mitral stenosis but it seemed incredible that such a condition could have developed in so short a time, and the diagnosis was held in abeyance. As convalescence progressed nothing was heard in the heart but a soft, blowing systolic murmur. Doubtless this girl eventually had the signs of organic mitral stenosis, but at the time we heard the presystolic murmur she probably had a functional stenosis due to edema about the valve ring and when the inflammation subsided the edema disappeared, and with it the murmur.

Winternitz and his associates have demonstrated the reason for the appearance and disappearance of these murmurs, but Sir James Mackenzie in reporting two such cases gives no explanation.

Basal systolic murmurs are principally heard at the so-called aortic and pulmonic areas. Not infrequently a soft, blowing systolic murmur is heard over the aortic area in the middle-aged and elderly, particularly among males, and is an indication of sclerotic changes in the aortic ring. The murmur is often transmitted to the pulmonic area and with diminishing intensity to the mitral region. It may have for a long time no accompanying signs, but more frequently there is some widening of the great vessels, a sharp closing of the aortic valve, an increase in the measurements of the heart, and some heightening of the blood pressure, particularly the diastolic. I have known physicians to interpret the aortic systolic mur-

mur as a sign of aortic stenosis but the murmur of that lesion is quite different. The latter is definitely limited in area, often no larger than the bell of a Bowles stethoscope, is rough and grating in quality, as stenotic murmurs are apt to be, is accompanied by a palpable thrill, absence of the second sound, and transmission to the vessels of the neck. The murmur of early stenosis may be very slight but with increasing obstruction to the blood stream it may become extremely loud, and when transmitted to the entire chest it may on occasion be heard a short distance from the wall with the unaided ear; in addition, there is the plateau or sustained pulse. With stenosis there is also regurgitation in most cases, and therefore a diastolic murmur.

The systolic murmur at the pulmonic area is frequently heard and is the commonest of all murmurs. It may be audible when the patient is lying down and not at all in the upright position. Unless it is heard with considerable intensity in both positions it may be classed as functional or physiological. The murmur is often of a soft, blowing quality, which begins early in systole and extends through most of it, but does not obscure the first sound; the pulmonic second sound is frequently accentuated.

The organic systolic murmurs in the pulmonic area are much rarer. The harsh murmurs of congenital pulmonic stenosis and acquired pulmonic stenosis have a very limited area and are usually accompanied by a rough thrill. The former condition is accompanied by cyanosis, a frail physique, easy fatigue and early cardiac failure, while the latter may be compatible with reasonably good health and a sense of well-being for many years. In the cases I have seen, the difference between the general condition of the patients with congenital lesions and that of those with acquired lesions is very striking. The nearness of the so-called "valve areas" and the similarity of the murmurs in aortic stenosis and pulmonary stenosis make the differential diagnosis sometimes quite difficult or even impossible. Other physical findings and history must be used to their fullest extent in such cases.

Cardiorespiratory murmurs are most commonly heard along the left border of the heart. They are usually systolic in time, very rarely diastolic. They are due to the pressure of

the heart against the lung during systole or to the squeezing of air from the lung during the contraction, or to old adhesions between the pleura and pericardium. Sometimes a history of pneumonia or a healed tuberculosis may explain it. Other physical signs will of course be absent and if it can be determined that the murmur is respiratory it has no importance. In like manner obesity, upward pressure of the diaphragm or tumors of the chest may be the cause of systolic murmurs. Over the base of the heart, aneurysm, dilatation, constriction from without, or any deformity, may cause murmurs in the great vessels as well as in the peripheral.

### THE DIASTOLIC MURMURS

The diastolic murmur is more difficult to hear than the systolic murmur and of much greater importance. It is occasionally functional without valve involvement when changes occur in the aorta in hypertension and arteriosclerosis. It is practically never an unimportant murmur, as is the systolic in numerous instances. It occurs in two organic conditions, aortic regurgitation and mitral stenosis.

In aortic regurgitation the murmur is soft and blowing; it may be heard over the aortic area or over the entire precordium, but it is usually of greatest intensity along the left border of the sternum at about the third and fourth interspaces. Because it occupies all of diastole it usually entirely obscures the second sound. In well-marked cases of aortic regurgitation there is lateral and downward enlargement of the heart with the cardiac impulse in the sixth interspace; throbbing of the carotids with head-nodding; pulsation of the retinal vessels; the characteristic Corrigan or "waterhammer" pulse; often a normal or high systolic blood pressure with a very low or almost absent diastolic pressure, giving the typical high pulse pressure of the lesion; throbbing of the femoral, iliac, posterior tibial and dorsalis pedis vessels with the typical sharp systolic shock known as the "pistol shot," heard with the stethoscope over these vessels, especially the femorals and iliacs; not infrequently over the iliacs systolic and diastolic murmurs are heard—known as Duroziez's sign. In most well-marked cases, especially with a high pulse pressure, there is a capillary pulse but a little care must be used in eliciting

this sign, as it may occur in some who have not aortic regurgitation, or even in normal individuals. The best method is to rub the forehead with a tongue depressor until it is hyperemic and as the redness begins to disappear the pulse may be seen as a rhythmically recurring blush. Do not stand too near the patient if you wish to see it to the best advantage.

Sometimes patients have entered the hospital with many of the physical signs of aortic regurgitation but the murmur does not appear until there has been a rest in bed for several days, when, with increased muscle tone, it appears with its usual qualities.

The earliest murmur of mitral stenosis is mid-diastolic, soft, blowing and often difficult to hear. In every case with an apical systolic murmur, especially if of sufficient duration, intensity and persistence, the mid-diastolic murmur should be carefully sought. All murmurs vary with the amount of muscle force in the heart, with the cardiac rate and with the rhythm. So the early soft murmur may be mid-diastolic where the rate is normal and the rhythm fairly regular; sometimes it may be late diastolic or it may be early diastolic, especially when it precedes and merges into the rough diastolic, ending in a sharp first sound, the murmur often spoken of as presystolic. Years ago the presystolic was considered the determining diagnostic sign of mitral stenosis—often the disease was not recognized until this rough, sometimes called crescendo, murmur was heard. It is accompanied by a thrill, a heaving cardiac impulse and by a radial pulse small in volume and of low tension. The thrill is also presystolic but too much effort need not be expended in determining its exact time—if it is fairly marked and accompanies a presystolic murmur, that is enough. It is agreed that the murmurs of mitral stenosis are caused by left-auricular systole and therefore they are soft diastolic at first, but as the warping and stenosis of the valve advance while the muscle force of the auricle remains fairly normal, the blood in passing through the narrowed opening causes a rough murmur and a palpable vibration. This roughness often disappears with dilatation of the auricle and with the onset of marked arrhythmia; in auricular fibrillation especially, the murmurs may be entirely absent or heard only in the longer diastolic spaces. When a blowing diastolic

murmur is audible at the area of cardiac impulse there should be little doubt about its significance—it is probably organic. Aortic regurgitation occurs at a valve opening which is concerned with the second sound of the heart and the regurgitant blood stream obscures the sound of its closure. The diastolic murmur of mitral stenosis occurs at a valve unrelated to the second sound, therefore is unobstructive to it. The shape of the heart, the position of the cardiac impulse, the character of the pulse, the sounds in the blood vessels are all quite different in the two conditions.

Sometimes young persons with thin chests, who are nervous about being examined, especially by a new physician, may present what appears to be a vibratory murmur accompanied by a thrill which later entirely disappears. Another condition producing a relative mitral stenosis without actual damage to the mitral valve is probably left-ventricular dilatation.

Two conditions seem to produce a relative mitral stenosis, more commonly aortic regurgitation and less frequently dilatation associated with adherent pericardium. Several theories have been advanced over the years to account for relative mitral stenosis. The time relations and other characteristics of the murmur are the same as in organic mitral stenosis, except that the murmur is usually less intense and is unaccompanied by a thrill. When the mitral diastolic murmur just described accompanies aortic regurgitation it is known as the Austin-Flint murmur. In cases of organic mitral stenosis associated with aortic regurgitation, the lessened volume of blood caused by the stenosis often has a modifying effect upon the Corrigan pulse but this is not the case with a merely functional mitral diastolic murmur.

Pulmonary regurgitation is very rare but its murmur has all the characteristics of the diastolic murmur of aortic regurgitation. While the latter is best heard along the left border of the sternum, the murmur of pulmonary regurgitation is equally loud or may be louder in the pulmonic area, but it is unaccompanied by signs in the peripheral circulation so characteristic of aortic regurgitation. Radiographic studies of the lungs for pulsations and abnormal right-axis deviation in the electrocardiogram will help to differentiate the pulmonary regurgitation murmur from the aortic. Mitral

stenosis, by causing increased pulmonary tension, and therefore dilatation of the pulmonary artery and valve ring without valve pathology, may cause pulmonary regurgitation and the diastolic murmur thus produced is known as the Graham Steell murmur.

Other causes which must be considered are acute or chronic endocarditis of the valve as illustrated by a case seen a few years ago with a gonococcus involvement of the pulmonary valve; chronic disease of the lungs; sometimes extended patency of the ductus arteriosus and congenital defects which give rise to regurgitation as a sequel of stenosis.

#### PERICARDIAL FRICTION RUBS

We have heard physicians debating the differentiation between double murmurs and the pericardial friction rub. The rub may be mistaken for murmurs, especially if the sound is soft, faint, and audible only in systole, where it is often heard much better, because contraction is more active than filling. If you listen very carefully during diastole you will hear an exactly similar sound, although at times much fainter. The unmistakable pericardial friction rub is rough and rasping during systole and of similar quality during diastole, and may be accompanied by a palpable thrill. Another important point is that pericardial rubs often change their position in the precordial area from day to day, as organic murmurs never do. When the friction rub is present it may obscure valve murmurs. Let me illustrate what I mean by the change in position of the pericardial rub, by recalling an incident reported some years ago. The quest for a case of aortic stenosis in the hospital resulted in my being shown a twenty-seven-year-old male patient convalescent from acute rheumatism and having the condition I was in search of, according to the diagnosis. The man looked well and said that all of his symptoms had subsided. On listening over the aortic area, a rough, grating, systolic murmur was heard and also a very faint murmur of similar quality in diastole. There were no cardiac nor circulatory signs indicating aortic stenosis or regurgitation. In the absence of confirmatory signs of valvular disease and taking into account his recent attack of acute rheumatism, a pericardial friction rub seemed probable. Two days later the

## SIGNIFICANCE OF HEART MURMURS

rough systolic sound and the fainter diastolic were heard the third interspace to the left of the sternum, the following day over the fourth and by the fifth day they were audible just above the cardiac impulse and then disappeared. In other words, there was no aortic stenosis, but there was pericardial friction rub. During acute infections, especially rheumatic fever, the precordium should be explored for friction sounds, knowing that they may be very transitory. Once heard, if only for a brief period, we should make a search for valve murmurs, since we know that myocarditis, endocardium and pericardium are probably all involved, though in varying degrees.

### TO-AND-FRO OR CONTINUOUS MURMURS

The commonest and least important of the continuous murmurs, one long known to physicians, is the venous hum of the neck. It is loudest at the base of the right side, less so on the left, is heard in many normal individuals, especially children, and is important to consider only because it may be transmitted to the base of the heart, where it may give rise to an erroneous diagnosis of aortic regurgitation, especially if the diastolic part of the hum happens to be prominent. In the absence of other signs of valvular lesions will disappear with the diagnoses.

Patency of the ductus arteriosus gives a see-saw murmur, louder in systole and best heard in the first or second interspace to the left of the sternum. Probably no other murmur has this continuous, grinding character throughout the cycle, and if it can be distinguished from the venous hum of the neck and arteriovenous aneurysms it is usually nomonic.

### SUMMARY

Murmurs are merely a part, sometimes a very small part, of the complete cardiac and circulatory examination.

Medical history should be thorough and searching, and aid in estimating the importance of any murmur.

During the course of acute infections, especially rheumatic fever, there should be no haste on the part of the physician attendant to reach a conclusion concerning a murmur. Convalescence may entirely change the cardiac findings.



If a murmur is heard during a routine physical examination, some information about it should be given to the patient or his relatives, because if it is passed without comment another physician at a subsequent examination may unduly alarm the patient and you will be considered remiss.

The systolic murmur is much commoner than the diastolic, easier to hear but often more difficult to interpret. The systolic murmur is more often functional than any other. The duration and intensity of a systolic murmur should be carefully studied. If the evidence points to a functional murmur the patient should be seen at regular intervals to substantiate the opinion, because it is well known that many systolic murmurs which are classed as benign because there is no other evidence of cardiac inefficiency, are actually the earliest indication of serious valvular pathology. The louder systolic murmurs are usually associated with organic cardiac disease.

If the physician keeps the normal physiology of the valves in mind he will not have to burden his memory with the time and character of murmurs produced by valve pathology.

Simple murmurs do not require treatment, while organic ones demand whatever the cardiac inefficiency requires.

## CLINIC OF DR. EDWARD S. EMERY, JR.

PETER BENT BRIGHAM HOSPITAL

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### THE DIAGNOSIS AND MANAGEMENT OF THE CHRONIC OBSTRUCTIVE TYPE OF PEPTIC ULCER

To treat successfully a patient with a peptic ulcer and chronic obstruction, one should know when an obstruction is in fact chronic and when surgery is indicated for its alleviation.

Ulcers may produce all grades of obstruction. There is the transient obstruction, which is obviously the result of a pylorospasm. Then there is the permanent type, which shows little fluctuation but may progress over a series of years. This kind of obstruction can be divided arbitrarily into two categories; the one which subsides on a good medical régime and the one that does not. A word should be said at this place about the cause of the more permanent types of obstruction. It has been taught for years that the obstruction which responds to medical treatment is the result of spasm and edema and that the other group is produced by a cicatrization of the pylorus. This teaching seems to have been based on pure reason without observation, for there is really very little, if anything, to substantiate the idea of a true cicatrization. In a recent conversation with a pathologist of wide experience, he stated that he had never seen a cicatrized pylorus due to ulcer. The late B. W. Sippy used to teach that retention disappeared on his treatment at the end of three months in 50 per cent of the cases and at the end of nine months in 85 per cent. Therefore, it is reasonable to believe that obstruction results from spasm and hypertrophy of the pylorus in most, if not all, of the cases. This complication should ultimately respond to medical treatment in virtually all cases, if

the treatment is persisted in thoroughly enough and long enough. Hence the former principle of treatment, that obstruction requires surgery because of the nature of the condition, does not seem to be correct. Surgery should be resorted to when it will relieve retention more easily than medical treatment, and thus save the patient time and spare him an adherence to a very strict and long continued régime.

The decision of when to use surgery may be decided on one or more of the following aids to diagnosis: (1) The roentgenographic findings. (2) Evidence from gastric aspirations of undue retention. (3) A history of obstructive symptoms. (4) The failure or otherwise for the obstruction to respond to medical treatment. In evaluating the use of the x-ray in the diagnosis of obstruction, one must remember that this method of investigation merely reveals visual evidence of what seems to be taking place in the stomach. The roentgenologist deduces from the available evidence whether or not an obstruction is present. One of his aids to diagnosis is the presence of retention, the amount of which is usually expressed in percentage of the total amount of barium ingested. Retention alone is not evidence for obstruction because complete retention may result from a lack of peristalsis. This situation occurs most frequently under the influence of a headache or emotion, frequently precipitated by worry over having the roentgenographic study.

The type of peristalsis is a further aid to the roentgenologist. Increased resistance to the outflow of the gastric contents produces more work for the stomach with a resulting hypertrophy of that organ. Therefore, marked grades of stenosis are accompanied by deep peristaltic waves. The presence of a large retention associated with increased peristalsis usually is good evidence for a so-called "high-grade" obstruction. However, since all degrees of hypertrophy may be encountered, and since hyperperistalsis in the absence of anything more than pylorospasm can occur, it is not always easy to differentiate between the two. In such situations a history of obstructive symptoms is useful evidence although not infallible. Some patients vomit more readily than others. It is not uncommon to find individuals with almost complete stenosis, who have never vomited, in contradistinction to others

who have been vomiting frequently without any chronic obstruction. The latter patients frequently suffer from an acute pylorospasm which subsides quickly on medical care. Enough has been said to show that a single roentgenographic examination may not tell much of practical value concerning the presence or the degree of obstruction. Except in those cases with a high-grade obstruction a second roentgenographic examination should be used to check the first.

As will be seen later, a knowledge of the amount of obstruction is important in deciding when to use surgery. Therefore, one is interested particularly in how the stomach handles ordinary food. Its behavior toward food is not answered by the usual roentgenographic examination. The usual barium meal is of a liquid or semisolid consistency, and the stomach behaves differently with liquids than with solids. Also the barium is an unusual substance to enter the stomach. It is a heavy mixture, the solid portion of which settles out quickly. It may flow rapidly through a narrowed pylorus or plug effectively this opening, depending upon the shape of the stomach. One would expect that the results from a barium meal might differ from an ordinary meal, and this has been found to be true.

A comparison of the roentgen and clinical evidence for retention in 266 patients seen at the Peter Bent Brigham Hospital showed an agreement between the two methods in 53 per cent. The closest agreement occurred with those patients which showed a large residue by the x-ray. Seventy-one per cent of those having from 30-60 per cent retention by x-ray also showed clinical evidences of retention, whereas, the results agreed even better when the retention by x-ray was over 60 per cent. Ninety-one per cent of the latter showed clinical retention. The 9 per cent showing a large roentgen retention but no clinical obstruction were the cases with reflex spasm due to headache, nervousness, etc. Disagreement between the results obtained by the two methods occurred almost entirely in the patients in which smaller residues were observed under fluoroscopic examination. These figures show that a single roentgen examination is not an accurate measure of how well the stomach can handle food.

Recognition of this fact is important, if one is to afford

suitable treatment for these patients, because clinical studies demonstrate that sole reliance on the x-ray does not give the best criteria for treatment. At the Peter Bent Brigham Hospital medical treatment was effective in only 38.6 per cent of the cases in which the gastric aspirations and the history agreed with the roentgen findings, whereas, it was of benefit in 68.2 per cent of the cases in which the roentgenogram alone suggested retention. The retention in many of the latter group was doubtless the result of temporary spasm. It is evident from this data that reliance on roentgen evidence alone will result in subjecting an unnecessarily large number of patients to surgery.

This difficulty can be offset by utilizing the final method of study that was mentioned, namely, putting the patient on a good medical régime. This medical treatment should be effective in overcoming the known causes of irritation, namely, the hydrochloric acid and the effect of prolonged gastric residues. This is accomplished most satisfactorily by a Sippy régime with gastric lavage every night and again in the morning, if there is found to be an increase in the fasting contents. This treatment should be continued if a large retention subsides quickly. The persistence of a large retention after a week to ten days usually means a marked obstruction and surgery might as well be used at once. Meanwhile, no time has been wasted because these patients do better if they are prepared with frequent gastric lavages.

Medical treatment should be continued for six weeks to three months on patients with moderate retention. Six weeks is a minimum period on which to gauge the effect of treatment, because it seems to require this length of time for moderate degrees of pylorospasm to subside. In fact, the first effect of medical treatment may be an increase in retention which later subsides. This phenomenon is caused in all probability by a decrease in excessive peristalsis before a decrease in obstruction takes place.

Three months usually is long enough to decide whether the obstruction is responding in a satisfactory way to medical treatment. Although most cases should respond ultimately, if one persists in treatment long enough, usually it is better to use surgery after three months, if very definite improvement

has not occurred. Some guide as to what constitutes a satisfactory response is given by the results obtained in this clinic. It has been found that the end-results of treating a gastric retention under 40 per cent is similar with medical or surgical therapy. Because this figure was obtained before patients had had any treatment, it is wiser to use a lower figure after medical treatment has been used. Hence, it is good practice to operate upon a patient who still has a 30 per cent retention by the x-ray after three months of good medical treatment.

This gives us a plan for treating ulcer patients with retention. One should employ surgery for patients with a gastric retention of 40 per cent or over, who have evidence of a long-standing pyloric obstruction, as shown by deep peristaltic waves due to hypertrophy.

Patients with a retention of 40 per cent or over but without evidence of hypertrophy by the x-ray should have a preliminary trial with medical treatment.

For the patient with a large original retention of 60 per cent or over, which may be due to either temporary inhibition of peristalsis or to obstruction, a period of seven to ten days on medical treatment usually is sufficient to decide which kind of treatment to use.

For all other patients with a retention of 40 per cent, medical or surgical treatment give equally good results.

The following illustrative case demonstrates what can be accomplished by careful medical treatment:

J. J. O., a fifty-eight-year-old rent collector, had had symptoms of ulcer for twenty years, when first seen in 1929. At the time he consulted us he was troubled chiefly by the rumbling of gas and fulness. He had not vomited. Physical examination was essentially negative. A roentgen examination reported a 90 per cent retention with an obstructive type of peristalsis. He was referred to the hospital wards and placed on a Sippy régime with aspirations each night. After four weeks of this treatment, the stomach was hypertonic, showed vigorous peristalsis, but the residue had decreased to 5 per cent. One month after discharge from the hospital the stomach still showed vigorous peristalsis and a 10 per cent residue. At this time he was given the choice of surgery or of continuing with daily aspirations, but he preferred to go on as before. He remained on a Sippy régime with daily aspirations for another year. He was then obtaining 750 to 900 cc. of gastric contents each night. Because the ulcer had given no symptoms for a year, the Sippy treatment was stopped, and the patient was put on a carefully supervised list of foods with five feedings a day. He continued this dietary treatment with aspirations every night for the next two years. For the last two years he has aspirated

only occasionally. The retention has steadily diminished until now he aspirates only 200 cc. three hours after supper, and there was no retention by x-ray at the last examination.

Most patients would prefer surgery to undergoing such a long and vigorous medical treatment, but the case illustrates that marked obstruction will respond to medical treatment and it is, therefore, always justifiable to determine the effect of medical treatment on obstruction due to ulcer before instituting surgery.

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### THE CLINICAL IMPORTANCE OF THE SEQUENCE OF EVENTS IN BONE MARROW FAILURE

ABNORMALITIES in the peripheral blood picture must be interpreted with caution and with due regard for certain physiological principles and clinical facts. In both hospital and private practice we not infrequently encounter patients with unusual blood findings which reflect but poorly the true underlying pathological condition, which may indeed be due to abnormalities in systems other than the hematopoietic. Blood pictures varying but little from the normal may be associated with the early stages of the most fatal blood diseases and, on the other hand, marked changes may be but temporary and not due to any fundamental or serious bone marrow dyscrasia.

The following cases illustrate certain points in diagnosis and prognosis which may be of interest to the clinician.

Case I.—A married woman\* of thirty-five years had been taking  $1\frac{1}{2}$  grains of dinitrophenol intermittently for the past year. During the two weeks prior to admission to the hospital she had taken approximately 21 grains of the drug and had lost 7 pounds in weight. Six days prior to admission she had an attack of acute tonsillitis, for which she was treated symptomatically. On the sixth day of this illness she appeared definitely worse and was taken to the hospital on May 14, 1935. Then, for the first time, her blood was studied. The white blood cell count was 900 per cubic millimeter; the red blood cell count 3,320,000; the hemoglobin 62 per cent. Examination of the blood smear

\* I am indebted to Dr. Stanley Imerman of Los Angeles for permission to cite this case.



showed 94 per cent lymphocytes and 6 per cent eosinophils. The platelets were slightly decreased. Her temperature was 104° F.; the pulse 130; the respirations 20. Both tonsils were enlarged, ulcerated, and covered with a grayish membrane. The soft palate, uvula and pharynx were acutely inflamed. Cultures for the throat were negative for diphtheria bacilli. The urine contained a trace of albumen, an occasional cast, and a few red blood cells. A diagnosis of agranulocytosis secondary to dinitrophenol therapy was made and the patient immediately started on pentnucleotide, 10 cc. intramuscularly four times a day. This she bore without untoward reactions. In addition 3 cc. of liver extract were given each day. Appropriate symptomatic treatment was, of course, continued and all dinitrophenol medication stopped.

From a clinical point of view she remained very ill, semiconscious and rational, but on May 18, four days after admission, the white blood cell count had risen to 1700 per cubic centimeter, and there were found in the smear 19.2 per cent polymorphonuclear neutrophils, 16.2 per cent monocytes, 61.2 per cent lymphocytes, 1.5 per cent eosinophils, and 1.9 per cent unclassified cells. The throat condition seemed definitely improved. The pentnucleotide was continued in full doses.

Three days later, on May 21, the patient's clinical condition was greatly improved and the temperature dropped to normal. The white blood cell count had risen to 4000 per cubic millimeter and the neutrophils were 35 per cent, but coincidentally the platelets had fallen to 30,000 per cubic millimeter. The red blood cell count was still 3,300,000 per cubic millimeter. Many petechiae were noted scattered over the body and in the mucous membranes. The platelet decrease, however, proved to be of an evanescent nature; for five days later the blood contained a normal number of these elements and there was no further hemorrhagic tendency. Moreover, the white blood cell count had then risen to 12,000 per cubic millimeter, and the polymorphonuclear neutrophils to 65 per cent. Pentnucleotide was then discontinued.

But by this time, two weeks after entry, the red blood cell count had fallen to 2,900,000 per cubic millimeter, and the hemoglobin to 56 per cent. A week later the red blood cell count had fallen still further to 2,500,000 per cubic millimeter. This slowly developing anemia, together with at least temporary marked reduction of platelets with attendant hemorrhages, aroused the suspicion that the condition was in reality a true aplastic anemia or pancytopenia and the fear was expressed by some that a fatal termination might be looked forward to. Such, however, was not my opinion. It may correctly be assumed in this instance that the dinitrophenol was the cause of the existing blood dyscrasia. It may further be assumed that on or about May 5 the toxic action of this substance had reached a sufficient degree to destroy or suppress, in large parts at least, the existing active bone marrow. The first outward and visible effect of such an action would be the partial or complete disappearance of the polymorphonuclear neutrophils, whose natural life in the peripheral blood is probably a matter of a few hours or at most a few days. This finding, together with the recognition of its significance, resulted in the withdrawal of the causative agent and the initiation of those measures which at present seem most likely to result in a stimulation of the granulocytic elements of the bone marrow. It is a matter of record that these cells did reappear in considerable numbers in less than a week. There was, therefore, tangible and unequivocal evidence that the bone marrow was recovering, at least in so far as the granular series was concerned.

With the red cell series the situation is quite different. The average life of a red cell in the peripheral blood is generally conceded to be from three to six weeks. The rate of formation of new red blood cells proceeds slowly; never with the dramatic suddenness with which white cells may be replaced. Under these circumstances it must be obvious that if a bone marrow is virtually wiped out by some toxic agent on a given date, anemia of moment will not make its appearance in the peripheral blood for several weeks. If, in the meantime, the noxious agent has been removed, if such measures as may be regarded as favoring bone marrow recovery have been instituted, and if there become manifest certain signs of recovery of the bone marrow, such as an increase in the white blood cell count, then it may safely be assumed that the anemia, such as developed in this case, is the natural and inevitable result of the original insult and need not necessarily be regarded as indicating the development of a further or more serious disease. Transfusions of blood under these circumstances are not, in my opinion, indicated unless the patient be in actual danger from the anemia *per se*. They may do more harm than good and severe reactions are not uncommon.

In late May, two and a half weeks after entry, the white blood cell count had risen to 13,000 per cubic millimeter and the neutrophils to 65 per cent. The temperature, which had been normal for many days, again rose. The patient developed a dry, hacking cough and complained of pain in the left upper chest. x-Ray films showed what appeared to be pneumonia in the left upper lobe. As time passed it became increasingly evident that the process was indeed a pulmonary abscess. For this complication general supportive and symptomatic treatment was instituted. In a month the abscess under this conservative régime, was but half its original size. In another month it had entirely disappeared. In the meantime, the red blood cell count rose to a normal figure and by July 13, eight weeks after entry, all abnormalities of the blood had disappeared and the patient was clinically well.

The lesson that such a case teaches is that the development of the various signs of bone marrow insufficiency become manifest at varying intervals after the original provocative injury; leukopenia in a few days, thrombocytopenia probably in a week or so, anemia not for several weeks. The natural history of recovering (or failing) bone marrow must be carefully considered in any diagnosis or prognosis.

The implications derived from such considerations are

broad. The late development of anemia following the action of a toxic substance on the bone marrow does not necessarily imply that some new and unexplained insult has resulted. In a similar manner the absence of anemia during the early stages of a blood disease does not necessarily rule out those conditions commonly thought of as being associated with profound and progressive anemia. This latter point is illustrated by the following case.

Case II.—On April 22, 1935 I saw with Dr. H. T. French and Dr. C. C. Stewart of Hanover, N. H., a boy fourteen years old. He had always been strong and well and led a normal and active outdoor life. The only fact of any possible moment in his past history was that in infancy his diet had, for a short while, been definitely inadequate and unbalanced. For several weeks prior to admission to the hospital he had seemed somewhat lazy and somnolent; he lacked initiative and was inattentive. On April 15 he had a severe headache and complained of anorexia, nausea, and occasional vomiting. There was no abdominal pain. On admission his temperature was 103° F. This gradually fell to normal in three days, only to rise again to 102° F. on the fourth day. On examination at this time (April 22) he was found to be a well-built, strong-looking boy, a little drowsy and listless, but rational and cooperative. There was a definite but minimal bilateral horizontal nystagmus. The remainder of the physical examination was essentially normal. There was no lymph node enlargement in any region. The spleen could not be felt even on deep inspiration. There was no tenderness, spasm, or masses in the abdomen. Neurological examination was normal except for a questionable stiffness of the neck. Neither lumbar puncture nor x-ray films of the chest revealed any abnormalities.

The red blood cell count was 4,800,000 per cubic millimeter; the hemoglobin 90 per cent; the white blood cell count 2500 per cubic millimeter with 90 per cent normal lymphocytes, 8 per cent polymorphonuclear neutrophils and 2 per cent monocytes. The neutrophils showed no evidence of toxic degeneration such as are so frequently seen in the presence of an infection. The platelets were normal in number and appearance.

The condition was, therefore, essentially one of unexplained leukopenia, neutropenia, and fever. Idiopathic agranulocytosis seemed out of the question. It is extremely rare at this age. Fever of moment in this disease is due to infection secondary to the leukopenia and this infection is almost always obvious on careful examination. No such infection was in evidence. Furthermore, no drugs had been taken which might logically have been regarded as productive of the leukopenia. Leukemia is usually accompanied by progressive anemia, bleeding and the finding of abnormally young cells in the peripheral blood; these features are almost constant once fever has set in. Yet it must be recognized that in leukemia of children there may rarely be but moderate departure from the normal white blood cell picture and, as pointed out above, anemia of any great degree does not develop under such conditions until after the lapse of several weeks. A diagnosis of leukemia in this case, therefore, could not be summarily discarded. It seemed, however, extremely unlikely and was not at any time seriously entertained. There remained the possibility of some obscure infection of uncertain nature and unknown locus. Such

a diagnosis would not advance our practical knowledge of the case in any way as long, that is, as its locus remained unknown.

The boy continued to run an irregular fever for three weeks. During this time the white blood cell count ranged from 1500 to 3000 per cubic millimeter and the neutrophils from 10 to 28 per cent. At no time were abnormal or immature white blood cells seen in the smear. Gradually his general condition improved. The fever abated. The blood picture became normal and he returned home apparently well on May 10, approximately four weeks after admission to the hospital.

He remained well until May 25 when once more his temperature rose, this time to 104° F. The initial symptoms of drowsiness reappeared and once more nausea, anorexia and vomiting occurred. Coincidentally the white blood cell count fell to 900 per cubic millimeter and the differential count revealed 100 per cent lymphocytes, all of them normal. The red blood cell count had fallen to 2,500,000 per cubic millimeter and the hemoglobin to 50 per cent. A new element, anemia of unexplained origin, had appeared. The physical examination was still essentially normal. There was no enlargement of the lymph nodes or spleen. Examination of the abdomen was negative. The elevated temperature continued and on June 3 reached 105° F. At this time there was definite soreness of the throat and the gums were found to be swollen and spongy. Retinal hemorrhages appeared in both eyes. A third element, the hemorrhagic diathesis, had appeared. The red blood cell count had fallen to 1,600,000 per cubic millimeter.

Now the significance of the anemia here would appear to be quite different from that in the first case. In that instance there was a definite and removable etiological agent which produced a sequence of events from which anemia was to be expected to develop even in the face of evidence of recovery on the part of the other blood elements. In the case of the boy we were dealing with a leukopenia of unknown origin and fluctuating course to which the subsequent development of anemia added further evidence of a serious bone marrow disease. It seemed evident, once anemia and thrombocytopenia had developed, that unless some definite and logical cause for the hematological abnormalities could be found one would have to assume a primary and probably irremediable bone marrow disorder.

Nevertheless, the temperature once more gradually came down to normal and there was definite clinical improvement. The white blood cell count rose to 2000 per cubic millimeter and the neutrophils to 24 per cent. The anemia, however, persisted in spite of intensive treatment with iron and liver extract. After this period of improvement the temperature again rose precipitantly, and the red blood cell count fell to 750,000 per cubic millimeter. Not the slightest evidence of regeneration of the red cell series could be found. The white blood cell count dropped to 500 per cubic millimeter, all granular cells disappeared, and the boy died in early July, three months after the initial symptoms.

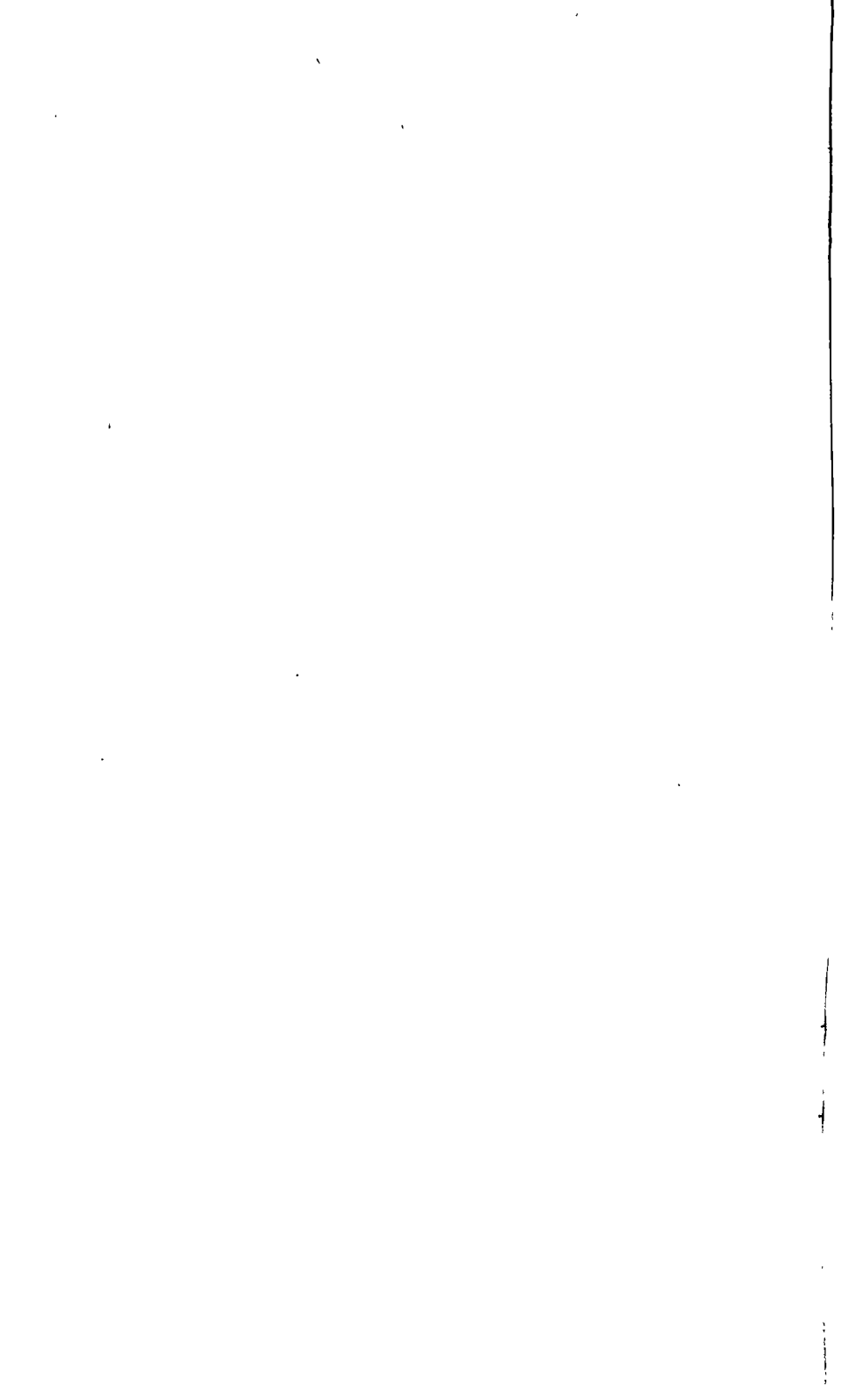
We are indebted to Dr. R. E. Miller of Hanover, N. H. for a study of the necropsy material. The positive findings were few. There was a chronic appendicitis with loss of the mucosa and masses of bacilli, some in phagocytes, in the superficial tissue. In addition, there was a slight periportal fibrosis of the liver, probably secondary to the appendiceal infection. From the appendix a bacterium of uncertain nature was recovered. The bone marrow was throughout aplastic and cell poor. There was no evidence of leukemic infiltration. On microscopical examination there was obvious a

marked hypoplasia of all the formed elements. Such few cells of the granular series as were present appeared normal. Erythropoeisis was scanty. There was no evidence of invasion by any malignant tumor.

While the case cannot be reconstructed with complete assurance, it would appear most likely that a slowly developing pancytopenia was the essential and primary lesion and that coincident with each period of marked neutropenia there was an exacerbation of the existing gastro-intestinal infection. Such an interpretation would be in accord with clinical experience. It may also be argued that the infection was primary and resulted in the pancytopenia, but chronic infection rarely produces such a blood picture when the clinical evidence for this infection is so slight as to be unrecognized during life and when postmortem studies reveal only a relatively mild and localized infectious process. Infection, when overwhelming, produces exhaustion of the bone marrow with evidence in the peripheral blood stream of ineffectual and spasmodic attempts at regeneration. On the other hand, drowsiness, nausea, vomiting and fever are common enough accompaniments of extreme leukopenia and of pancytopenia and it is important to remember that in this latter disease the process does not steadily progress with smooth regularity, but rather by a series of remissions and relapses. It is important, further, to remember that all the formed elements are not simultaneously or equally depressed. As a rule the white blood cells suffer first, the red cell series second and the platelets last, although of course there are many exceptions to this general rule. Moreover, in the presence of leukopenia, even of the most transient sort, any existing infection may advance apace, to subside again as the primary defense against infection, the leukocytes, is reestablished. Taking all the evidence at hand, it would seem most logical to assume the presence of a progressing pancytopenia of unknown pathogenesis with a concurrent and secondary gastro-intestinal infection. In any event, extreme leukopenia and neutropenia in the presence of fever must be regarded as ominous, even though the phenomena may appear to be transient. We should be guarded in our prognosis, even though there be no anemia, remembering, as in the first case, that it takes time for such to develop.

In brief, one cannot or should not interpret the whole

clinical picture from a cross section of the blood abnormalities at any one time. The natural history of the failing and the recovering bone marrow must be taken into consideration. The fluctuating and remitting course of the early stages of serious bone marrow disorders must be recognized. No matter how striking the blood changes are the condition may be remediable; no matter how insignificant they may seem they may reflect the onset of a fatal condition.



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PAIN IN THE REGION OF THE HEART

**Introduction.**—We shall deal in this paper with pain in the region of the heart that is not angina pectoris. The difference between pain or distress in the region of the heart and angina pectoris will not be discussed, because descriptions of angina pectoris can be found in many textbooks and a repetition is not needed.

The pain or distress in the region of the heart with which we are concerned not only is not angina pectoris, it is nearly always not a symptom of any organic disease, and is usually definitely neurotic. This statement will surprise very few. Physicians generally are familiar with the fact that pain in the region of the heart, even when it is of great severity, may be a neurosis. Nevertheless, we find that such pain, when encountered clinically, is so disturbing that it frequently causes physicians, particularly when they have it themselves, even though they are technically familiar with cardiac neurosis, to believe that the pain must be an indication of organic heart disease when it is not. The need for correct diagnosis is clear. There is a vast difference in the treatment of cardiac neurosis and cardiac disease. We could cite many case histories to show that errors of judgment in either direction may be disastrous. In this connection, we find that minor errors in diagnosis and treatment are often caused by a failure to appreciate that neurotic pain in the region of the heart may occur coincidentally with organic heart disease. In fact, neu-



roses are proportionately higher among those who have organic heart disease. Cardiac cases naturally have their attention directed toward and their anxiety aroused by the action of their hearts. Often, for example, a patient with mitral stenosis consults a specialist not because of symptoms due to the mitral stenosis, mitral stenosis may give no subjective symptoms whatsoever, but because the patient, knowing of the heart disease and its dangers, develops neurotic symptoms suggesting to all concerned an alarming situation. We also believe that, in spite of its importance, cardiac neurosis has been neglected. We seldom find it demonstrated in clinics or discussed at scientific meetings. It is a confusing topic and, therefore, perhaps avoided. We believe a discussion of it is in order.

**Terminology.**—People suffering from vague symptoms, including pain in the region of the heart, which we nowadays definitely label neurotic, symptoms which tend to be confused with symptoms of organic heart disease, have long been recognized. Terminology has contributed to the general confusion concerning them. The inept term “functional heart disease” was formerly used to classify these cases and indeed we find it still used at times. During the World War these cases were vigorously studied, and this term was abandoned. The names “soldier’s heart,” “disorderly action of the heart,” “effort syndrome” and most apt of all, “neurocirculatory asthenia,” were applied to them. We will use this last term for the remainder of this article, abbreviating it to its initials, N. C. A. This term is generally somewhat familiar.

A distinction has been made by some observers between “cardiac neurosis” and “N. C. A.” on the basis that in the former there is no objective evidence of cardiovascular disturbance. We believe it is inappropriate to try to make such distinction since our cases grade evenly from one class to another and individuals change their symptoms so that one would have to reclassify them from time to time. We would refer to N. C. A. including those patients who would be called “cardiac neurosis” by those who wish to attempt a distinction.

**N. C. A. Among Soldiers.**—Study during the war was forced by military and economic necessity. In England alone, at one time, 30,000 soldiers were in hospital supposedly com-

pletely disabled by N. C. A. Physicians found themselves unprepared for these vast numbers of disabled young men with symptoms referable to the heart. The disorder did not resemble clearly anything with which they were familiar in civil practice.

In brief, the disturbance was as follows: soldiers who had it typically found themselves unable to carry on because of exaggerated feelings of extreme fatigue; they fell out of line of march and dropped at drill. Though the symptoms differed in individuals, in general they complained of stabbing or tearing pains at frequent intervals, usually below the heart, rarely throughout the chest or down one or both arms. Their hearts raced often at a terrific rate, sometimes more than 150 beats per minute. If exercised on a flight of steps, or by 100 hops, their pulse rates did not return to within 10 beats of the preexercise rate after a two minute rest; they thus showed a poor response to effort. Their blood pressure might be unobtainable when they first stood up, but within a few seconds or minutes would climb to a high systolic level, often with a relatively low diastolic level. Some fainted suddenly and remained unconscious for as long as twenty minutes. They trembled so that some could not stand at attention, and had a sense and appearance of anxiety, of "impending calamity." They were breathless on slight exertion and spoke of a sense of suffocation; tachypnea was the rule even at rest. It was noted that their hands, feet and ears tended to be cyanosed, their extremities were cold and they sweated freely. Of course "myocarditis" was the first diagnosis considered. But direct examination of the heart showed no familiar signs of heart disease in the vast majority of cases and it was found that rest was bad for them while exercise helped the majority of them. After a six weeks' course of graduated exercises and drill, roughly 20 per cent of these soldiers seemed able to return to full duty, 20 per cent appeared completely disabled, while the remainder could carry on some degree of duty. Furthermore, these individuals never developed heart failure, no matter how breathless or exhausted they became. No matter how severe the heart pain they never died. So myocarditis as a cause of the symptoms had to be rejected.

Hyperthyroidism was clearly suggested by some of the

symptoms—rapid heart, tremor, increased fatigability. But the patients never developed clear signs of toxicity referable to the thyroid gland, and this possibility was also rejected.

No disease appeared to be closely associated with the condition. The most that one could say was that the incidence of chronic infections, in particular tuberculosis, was somewhat higher among these N. C. A.'s than in the general population. To be sure, N. C. A. symptoms in some cases occurred for the first time or were aggravated by *convalescence* from acute disease or injury. So the effect of organic disease or physical trauma in initiating the symptoms could not be ignored even though it was clear that organic disorders or their late effects could not account for the great majority of the cases. The symptoms were the same where there was no apparent cause, or when they followed *pneumonia*, *rheumatic fever*, *trench fever*, *battle wounds*, *shell shock*, *a drunken debauch*, *promotion*, *demotion*, or *bad news from home*.

Five years after the war it was found (2) that 33 per cent were improved or well, 3.2 per cent had become worse. The condition of the remainder was stationary. This must not be taken as a guide for prognosis for N. C. A. in civil life. Any familiarity with the severely disabled N. C. A. soldiers shows the unfortunate fact that they are more secure if they remain disabled. Feeling their inadequacy, they dread to be pronounced well and forced to take care of themselves. Reassurance can have little effect. And indeed one can only reassure them half-heartedly. There is no certainty that they will succeed in being well if they try.

Follow-ups have shown that these N. C. A.'s were good life insurance and operative risks.

**N. C. A. in Civil Life.**—It was through the study of soldiers that a solid, though inadequate, basis was established for the understanding and handling of patients with N. C. A. encountered in civil practice. For a few years after the war, occasional reports and studies of this condition appeared, but for the past fifteen years it has been seldom dealt with in lectures or medical publications. We are forced to turn to the older descriptions for reference and we do not often recognize in them the condition we now encounter, for individuals who match the wartime cases in severity of signs and symp-

toms are now rarities. This may be because in civil life we rarely have anything analogous to the war as a cause of sudden and tremendous psychic shock among relatively young people and one can usually more readily escape from the severe tensions that do come in civil life. The symptoms of N. C. A. as encountered today are less dramatic and, at the same time, less clear cut than the war cases. Nevertheless, they are often as disabling and sometimes the symptoms are as severe as ever.

The symptoms of civilian N. C. A. are so various and vague that a thorough description would be difficult and undesirable. We find they are best described by illustrative cases presented against the background of their social and economic environment. We will later give such cases. Certain symptoms, however, occur so consistently that we will mention them. Of course, "heart pain": it grades in severity from a merely uncomfortable sensation or consciousness of the region of the heart or of the heart beat to precordial soreness and stabbing or pinching pain, sometimes of great severity. Such pain is by itself strong evidence of N. C. A. A complaint of breathlessness which really consists of sighing or a sense of inability to get enough air in the lungs, is also a clear sign of N. C. A. The precise value in diagnosis of other common symptoms and signs, such as great fatigability, breathlessness, tremor, cyanosis and tachycardia or poor response to effort is much less.

Curious case histories could be given where violent dyspnea or uncontrollable tremor or repeated fainting or complete helplessness from sudden sense of weakness were the outstanding complaints of cases severely disabled and suspected of heart disease, though the symptoms were purely neurotic, and were relieved by proper treatment. But such cases are comparatively rare. The most common outstanding complaint of the N. C. A. today is some degree of pain in the region of the heart.

#### CASE REPORTS

Case I.—This patient is a forty-five-year-old busy surgeon who married rather late and has 2 small children. His father died of angina. The patient has frequently made a correct diagnosis of cardiac neurosis on his own patients, nevertheless, he reported for examination with a look of despondency and weariness and, placing his hand beneath his heart said, "I'm done. Angina."

He also complained of precarious sleep and a general sense of fatigue and numerous minor symptoms. Physical examination was negative except for a left inguinal hernia. He had had this for a year, shortly before the onset of his heart pain. It had prevented him from exercising, with the result that he had gained greatly in weight and was in "poor condition." He had, however, "always kept putting off an operation." He feared that he would have an embolus and die. He was advised to take a three months' vacation. There was improvement but only for a few months. A year later, he consented to the hernia operation. As soon as he recovered, his symptoms disappeared and he began to engage in active athletics. He has remained well for several years, though on questioning says that he has little echoes of his pain when especially worried. And, like many physicians, believes that eventually he will die of angina. Many do.

**Case II.**—This is another physician, thirty-two years old, married with one child, who has been engaged in practice for five years, and through unremitting hard work is now succeeding. He has a good family and past history and no vices. He states that "for the past several months, I have frequently had a sharp stinging pain just under my heart, lasting a few seconds. I am sleeping badly. My wind is not as good as it was. I have been staying up late working and have stopped regular exercise during the last 2 years and have gained a lot of weight. I have never had rheumatic fever, but will you listen to my heart?" The examination was negative, and when he had been reassured and put on a proper schedule of hours for sleep, exercise and diet, his symptoms vanished. When asked several years later about these symptoms, he failed to recall that he had had them or that he had consulted one of us.

**Case III.**—This patient is a healthy, attractive young woman of twenty-seven, the mother of one child. Her husband had left home to develop an artistic talent. He stayed longer than was expected. There were rumors of unfaithfulness on his part. The patient developed disturbing heart pain and consciousness of her heart beat which frequently was very rapid and forceful. There was breathlessness, easy fatigability and sleeplessness. These continued in spite of reassurance and a hygienic régime until she obtained a divorce with a financial settlement and retired with her child to live with her parents. Even then, there were milder recurrences until she was married to another, but since that time she has remained well.

**Case IV.**—This patient is a psychiatrist of seventy-two years, charming and intelligent, who had lived a successful life without special hardships, illnesses or disasters. He stated that "I awakened frequently this last winter, and am conscious of my heart beating hard at times and of a sense of soreness around the precordium coming and going for days at a time. On occasion, I have the sensation that I am suffocating and desire to take a full breath. I am fatigued. I come to you to see if I have heart disease or a mother-in-law complex." He did not have evidence of heart disease; he did have a mother-in-law, aged ninety-two, who had come to live in his home and who was a source of increasing anxiety, but he also, though past the age of retirement, was continuing his work and lectureship from year to year, while constantly before him was the unexpressed question, "when shall I break?"

The neurotic symptoms disappeared with explanations and he resumed work with comfort. But the inevitable break came without warning a few years later with an entirely different set of symptoms.

**Case V.**—Again we are dealing with a physician, a teacher and consultant of forty, who has never been sick and states that he is not nervous. There have been no disasters in his life, he has a happy home, several children and is successful in his profession. For a few months, he had noticed growing fatigability and breathlessness at his accustomed tasks and stabbing pains and a sense of soreness around the heart. Physical examination revealed no abnormality. He was reassured and discussion resulted in the idea that he was not getting enough exercise or rest. This was corrected but no improvement occurred. He then gave up smoking, in which he had indulged heavily, and still he was no better. Finally his teeth were x-rayed; three badly abscessed teeth were found and removed, and within three or four days, he experienced complete and lasting relief from his symptoms.

**Case VI.**—This woman, now over fifty, was seen by one of us ten years ago as the eighth consultant on her case. She was married, had 2 children and her environment was pleasant and easy. She had a normal inheritance except that a grandmother had been a cardiac invalid for thirty years. She herself had been kept out of school for a year when fourteen years of age with "anemia and myocarditis," but otherwise had had no significant illnesses. Her 2 children were born within two years of her marriage. Twenty years ago, following her second and last pregnancy, she began to suffer from frequent attacks of severe stabbing pain over the precordium, together with consciousness of the heart beat. Her heart rate, whenever taken, was found to be 120 beats per minute or over. There was weakness, easy fatigability and breathlessness. In addition, she suffered from vague digestive disturbances. These symptoms had persisted to the date of this examination. Her symptoms were such that she was only able to be up about six hours a day and felt that she had to be driven everywhere she went. She supervised her home and children but could do no work. She had no particular relaxations although she read a good deal. Her life with her husband was apparently congenial.

Her physical examination was quite negative, except for the tachycardia and some acrocyanosis. Treatment proved unsuccessful. A recent report from her family physician stated that her condition is still unchanged.

**Case VII.**—This patient is a thirteen-year-old girl. Since the death of her father from angina when she was eight years old she and her mother had lived with a grandmother. During this time she has slept with her mother. The patient's catamenia commenced six months ago. Her symptoms extend over this six-month period. She began by disliking school; she trembled, and felt faint and breathless at meeting people. She had soreness around the heart and frequent stabbing pains. Her heart raced at times. She dreamed, dreams of the anxiety type, frequently. She would hardly allow her mother out of her sight. One night, while her mother was attending a club meeting, she experienced an attack of heart pain so severe that a physician was called at once. He told the mother that he feared the child was suffering from rheumatic heart disease and that she would have to remain in bed for an indefinite period of time. Treatment by digitalis, vitamins and heliotherapy was given, but the symptoms became worse. A grave prognosis was given. The mother gave up all outside activities and devoted nearly every moment to her child.

The symptoms increased. There were tantrums, fainting spells, blurring of vision and transient hemianopia. The child had written poems for years; the poems had grown more mature as she grew older. She continued to write, but now the content of her poems reverted to nursery rhymes.

During the six months of her illness the grandmother had scolded the child and mother persistently, advising the mother not to spoil her daughter, to go out more and not to stay home and act as nurse. When the physician was appealed to, he was distinctly apprehensive regarding the child's heart and insisted on complete rest. (The physician, an experienced and able practitioner was not a poor diagnostician. He was faced with a situation which again and again is found alarming by other able men.)

Physical examination of this child was negative. In spite of the severity of the symptoms and the difficulties of the situation, brief but unreserved discussion of the case with mother and patient together was followed by almost complete relief of symptoms and a return to normal living which has lasted for a year.

**Discussion.**—These above cases are chosen as typical. The essentials of each are found in many others. With the possible exception of Case V, none had any organic disease which could directly cause the symptoms, and all had sound cardiovascular systems. In regard to most of them, factors in their lives producing anxiety states could be readily ascertained, although these factors had not been appreciated by the patients themselves. Thus in one patient, Case I, it was an unsuspected dread of death from a needed but postponed operation; in another, Case III, a disturbance in her relationship with her husband; a third, Case IV, was apprehensive of the breakdown of old age; while a fourth, Case II, was in poor physical condition from overwork and under-exercise and sleep. In Case VII an intricate and demanding attachment to her mother and jealousy for her attentions led to a state of complete invalidism at adolescence. Only in Case VI, the sole one which did not respond to treatment, are the factors producing the psychic disturbance hidden. In handling N. C. A.'s in general, it is not often necessary to resort to the radical therapy of such workers in abnormal psychology as Freud and Adler, but it is by no means wise to dismiss their theories as never applying. In the more serious and resistant cases, such as Case VI, therapy along these lines may offer the only hope of relief. One wishes that this patient (Case VI) had been analyzed.

Focal infection, as in Case V, appears definitely as an exciting cause now and then, and effective treatment is dependent on its removal. But focal infection is not demonstrable in

the majority of instances, and attempts to cure all by finding and removing obscure possible foci of infection repeatedly end in failure.

Thus, the ordinary *wear and tear* and *vicissitudes* of life with their resulting *anxiety* states, *bad habits* of living, and, to some extent, in a few *inheritance* appear as the exciting factors in most cases. N. C. A. may occur at all ages in both sexes, in all social conditions and among those with all degrees of mental ability. These individuals are usually not constitutionally "neurotic" unless we apply this term extremely widely. It is very common among physicians. Most of the patients get well.

The diagnosis of N. C. A. rests on the recognition of the peculiar nature of the described symptoms. It does not depend on the exclusion of organic disease. It is not made by physical signs or tests.

No matter how elaborately we develop routine physical examinations and laboratory tests, the diagnosis of this common condition can only be correctly made from the personal judgment of an enlightened physician. Though in the great majority of cases the diagnosis to an experienced physician is easy; there are occasional cases that make even those who deal with these cases daily wish to shift the responsibility, and that keep us awake nights. We do not often worry for fear we may be overlooking a serious heart disease. Pain in the region of the heart can, of course, be caused by pericarditis. It may in rare instances be caused by pressure from a greatly enlarged heart, though cardiac enlargement as a rule causes no pain. But, aside from these, pain such as we are concerned with is not caused by obscure heart disease. But there are rare, sometimes serious organic diseases, that can give pain in the region of the heart that is not angina and that neurosis may simulate. Following are some of these rare diseases that, in our experience, have caused severe pain in the region of the heart. The principal lesions, not cardiac, *above the diaphragm*, which we have found in our private consulting practice as a cause for precordial pain are: mediastinal, lung and esophageal tumor or diverticulitis, diaphragmatic hernia, pulmonary embolus, and cervical arthritis. *Below the diaphragm*, disease of the stomach, gallbladder, duodenum and pancreas. One some-



times reads of obscure chest pain which is labeled "pleurodynia," as though this was a specific disorder. We have never allowed ourselves to make such a diagnosis. Patients frequently believe and are encouraged to believe that pain in the region of the heart is due to pressure from gas in the gastrointestinal tract. This explanation serves to distract the patient's mind and to relieve apprehension. But it commonly causes cribbing and belching and resort to various remedies, not always harmless. And, sometimes, the result is a real discomfort from gas pressure. We should remember that pain in the region of the heart is nearly always neurotic. Gastrointestinal discomforts are common symptoms among neurotics. Bad habits, cathartics, cribbing, unnecessary dosing are easily induced.

Because of the similarity between the symptoms and signs of N. C. A. and those of hyperthyroidism, the latter condition should always be considered and eliminated, if necessary, by a basal metabolic rate determination. It is often wise to take the basal metabolic rate on an evident N. C. A. in order to convince the patient that hyperthyroidism is not present.

N. C. A. as seen today is treatable and the prognosis, on the whole, is good. The great majority of patients get well quickly, often with no more therapy than reassurance. A small proportion, possibly 10 per cent, tend to be prolonged with a tendency to recurrence. A few remain fixed for years, perhaps for life. But even the most prolonged and intractable cases sometimes suddenly get well. We cannot handle them all alike, though some need following indefinitely, many are cured at once with reassurance and should not be encouraged to remain under surveillance, which, in itself, may be poor therapy.

The general principles of treatment are reassurance, repeated as often as needed and as convincingly as possible, and a régime of diet, rest, exercise and work suited to the individual. Drugs, in general, are not indicated; digitalis and the other specifically cardiac drugs do no good. Occasionally, in selected cases, sedatives may be used temporarily to combat excessive nervousness or sleeplessness. But, in our opinion, the use of sedatives ought usually to be considered as an evasion. Explanation and reassurance rather than narcotics are

in order. Any reasonably correctable defects, such as infected teeth, should be corrected.

They should have time for sleep and time for rest and relaxation during the day. But they should not be put to bed. Sometimes a long overdue vacation is helpful, but, in general, it is possible and desirable to get the patient well *while* at work, regulating the daily régime so that the patient does not *overwork* and does stubbornly follow the rules of bodily and mental health in spite of doubt and discomforts. Diet should be adjusted to maintain the patient's weight within proper limits. Vague digestive disturbances, mentioned above, frequently require a nonirritating diet. Habits of cribbing, and poor bowel management often need correcting. On the whole, elaborate schedules of graded exercises such as were developed for the war cases has proved neither necessary nor especially helpful in civil practice. It is exceedingly difficult to apply such schedules thoroughly to patients who cannot be observed and controlled like soldiers. Treatment of N. C. A. by the more elaborate forms of psychiatry, such as we mentioned in discussion of Case VI, especially psychoanalysis, has been little tried as yet, but keeps suggesting itself as a logical possibility. Because of expense and time, psychoanalysis cannot be widely used by a cardiologist or an internist. And we should remember that we know that it is not necessary to resort to such heroic methods for satisfactory results in the great majority of cases. It is possible that in the future, the rare intractable cases will be recognized and come promptly under the case of a psychiatrist, while the cardiologist, becoming more versed in the technic of psychiatry, may be able to handle the usual cases in a more comprehending fashion. One hopes that more enlightenment from modern psychiatry will enrich what we now cherish as hard won common sense in the treatment of these common neurotics and not lead us to costly errors, as have other theories that explained the neuroses on the basis of some organic disease.

**N. C. A. Complicating Organic Heart Disease.**—Finally, we should like to cite two cases with N. C. A. and with organic heart disease. It must be remembered that patients with organic heart disease or, indeed, any disease, may in addition have N. C. A. These N. C. A. symptoms may be the real cause

of a disability, and may be totally unrelated to the organic disease. We were surprised recently to find that 20 per cent of a large series of young women with mitral stenosis seen in private practice complained of heart pain which was exactly like the pain described by patients with sound hearts who had N. C. A.

**Case VIII.**—The patient is a young woman, aged twenty-three, who was three months married and three months pregnant. She had no knowledge of any cardiac defects. She led a normal life with much exercise. She stayed up all one night at a dance, drank a little. Then during sexual intercourse became breathless, orthopneic, and raised pink-stained sputum. Orthopnea and breathlessness with signs of congestive heart failure continued for several hours and cleared. Seen the following day, her physical examination was negative except for mitral stenosis. Since then the patient has led a symptomless life with careful restrictions for twelve years, and has had 3 successful pregnancies. Following the death of 1 child by accident, she developed *severe* pain for the first time in the left chest in front, particularly below the heart and in the axilla. She became conscious of her heart beat, which was rapid. She frequently felt a desire to take a deep breath. She had anxiety dreams.

The physical examination showed no evidence of congestive failure and no change in her heart condition. Reassurance and explanation diminished at once the severity of her symptoms without change in her régime.

**Case IX.**—This patient, a woman of forty-two, who had rheumatic fever in her youth, but following this led to a normal life, was married and had 2 children. Following the birth of the second child, "she did not regain her strength," but suffered from breathlessness at her accustomed tasks and complained of a great sense of fatigue and of sleeplessness and precordial pain. She was seen in consultation at this time (twenty years ago) by an able cardiologist, now retired, who found mitral stenosis and apparently interpreted this as the cause of her complaints and stressed merely the necessity of a cautious régime on her and her husband. For twenty years the patient was up only a few hours a day, rarely went out, and was almost constantly conscious of her heart. Distressing precordial pain was the most prominent of her many symptoms. She never developed congestive failure. Suddenly, after twenty years of cardiac neurosis and no heart failure, without warning, she developed a right hemiplegia, probably from an embolus broken off from a thrombus formed behind the stenosed valve. She recovered partially from the paralysis, but her personality clearly changed. She became cheerful, fearless, free from complaints. There was no more mention of consciousness of the heart and heart pain. She struggled about the house doing more work than she had done at any time for the past twenty years, and remained up all day. This state continued until the patient was lost sight of several years later.

**Discussion.**—Case VIII explains itself.

Case IX shows the results of a misinterpretation of symptoms. If the cardiologist who first saw her had appreciated that her complaints were not due to her mitral stenosis, but

to cardiac neurosis and given proper treatment, she probably would have been improved or cured of the N. C. A. The abrupt cessation of her N. C. A. symptoms following the embolus offers a chance for speculation to those addicted to speculation on these matters. Did the embolus by causing organic change in her brain cells change her personality? Or did the obvious physical handicap of her partial paralysis provide her with a better excuse for invalidism (or outlet for her maladaptation if we prefer) than did her less obvious neurotic symptoms; and did these N. C. A. symptoms disappear because she no longer needed them? At any rate, we are satisfied for the purpose of this paper that for twenty years the patient, though possessing mitral stenosis, really was disabled by poorly treated N. C. A. and that, following the onset of an additional and organic disability, she lost her N. C. A., did more, and was happier. Such sudden changes in personality in prolonged N. C. A. appear to occur at times without any recognizable cause, psychic or structural.

**Summary.**—Several cases complaining chiefly of pain in the region of the heart have been presented and discussed. The facts have been stressed that pain or distress in the region of the heart that has no association with angina pectoris or coronary occlusion, is common. It is rarely organic. It is usually neurotic. It may be disabling. It is successfully treatable in the vast majority of cases. We have discussed the general management of such cases.

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### THE CURABILITY OF POLLEN HAY FEVER

PRESEASONAL treatment for pollen hay fever offers a cure, provided that the proper pollen extract is used; careful tests are made and judgment is employed in the manner of treatment. Two very important facts that are essential to successful pollen treatment are: that the patient must be accurate in his statement as to when and how long he has hay fever symptoms, and that the physician must know what plants are shedding pollen at that particular time in that patient's environment. A third important fact is to test the patient very carefully and accurately with those pollens which are prevalent during the patient's hay fever season. Another essential is a proper procedure of treatment and, finally, extraneous conditions must be taken into consideration for each patient. These important considerations will be discussed in detail.

**Hay Fever Seasons.**—The time of year or season when the patient has pollen hay fever falls into one or more of three periods, namely: spring, early summer, and late summer or fall. Naturally, the time of year that these seasons occur varies for different parts of the United States and more especially for foreign countries. For example, in New England the early summer season, during which the grasses pollinate, extends from the middle of May to the middle of July. Farther north this season is delayed two weeks, and as one goes south this season gradually advances. In Florida, a grass is in pollination in January; in Texas, cedar trees pollinate in January; in Venezuela, grasses pollinate in January. Rainy seasons in some parts of this country and foreign countries as well as cold winters in this country and Europe naturally permit of a resting period for pollination.

During the spring hay fever season, which in most parts of this country extends through March, April and May, the trees pollinate in a series. Since each tree completes its pollination in from one day (the pine) to several days (the oak) a patient must be sensitive to the pollen of more than one tree in order to experience much pollen hay fever at this season.

During the early summer season, May, June and July, the various grasses pollinate and they may cause hay fever for a period of six to eight weeks. The grass pollens are the cause of hay fever in from one quarter to one third of all cases of hay fever and the symptoms are severe. It is noted that in May some of the late pollinating trees and some of the early pollinating grasses coincide, therefore, these two seasons overlap. After the grasses have finished pollination there is in most localities a brief respite from pollen hay fever; it is a period of two or three weeks before the late hay fever season starts.

In the late summer, August, September and early October, the compositae, more especially the ragweeds pollinate. These are a profuse pollinator, cause severe hay fever symptoms for six or eight weeks and are responsible for about two thirds of all the hay fever cases.

Occasionally patients are sensitive to pollens that occur in all three seasons; more often to those pollens that occur in both early and late summer, or early summer alone, and most frequently to the pollens of late summer only. Certain grasses, for example; Bermuda grass, which pollinates after it has been cut two or three times a year, may be in pollination during the late hay fever season. Corn, which belongs to the grass family, pollinates, depending upon when it is planted, from late May to the middle of August. Although the pollen of corn does not contaminate the air which one may breathe, it does fall upon the silk and husks of the ear. Therefore, a patient who is sensitive to the grass family may have attacks of hay fever from husking corn during August and September, when the compositae are in pollination, and without tests ragweed pollen would be blamed for the cause.

All plants as regards pollens, are divided into two classes, namely: those whose pollens are borne by insects and those that are borne by the wind. A more practical division is,

those that are fragrant and pleasing to the eye and those that have little or no fragrance and little or no beauty. Those plants which have fragrance and beauty are cultivated and are insect pollinated, rarely cause hay fever. The pollen is heavy or sticky and is not dislodged by wind or air currents while in their normal condition. When such blossoms are cut from the plants and kept in a vase for a few days they may dry and considerable amounts of pollen may be blown about by drafts. However, such instances cause symptoms of only a few days' duration. Wind-borne pollens naturally lodge everywhere, even on blooms of non-hay fever causing plants so that the act of smelling of a rose in early summer may cause the inhalation of grass pollen, or in the fall, of ragweed pollen. Consequently, the patient's statement as to the cause of his hay fever may be very misleading. Roses are rarely the actual cause of hay fever and the same is true of golden rod, both of which are often suspected. The pollen of golden rod and daisy is sticky and does not blow about and consequently these do not cause hay fever in their natural habitat. The same is equally true of asters, golden glow, zinnias and fruit trees, etc.

The wind-borne hay fever-producing pollens are from plants that have inconspicuous blooms with no fragrance nor beauty, no qualities to attract insects and they produce nothing that insects desire. Examples of this type are non-fruit bearing trees, the grasses, ragweeds, tumble weeds, etc.

**Geographical Distribution of Pollens.**—A complete geographical distribution of hay fever pollens is out of the question in this paper. However, a brief survey may be of interest and helpful.

*In the East Coast States.*—As far south as North Carolina the spring season of hay fever, during March, April and May, concerns the willow, maple, oak, birch and poplar trees. The early summer season, from the middle of May to the middle of July, concerns only the grass family. June grass pollinates usually from the middle of May to the middle of June. Very few patients, however, are sufficiently bothered by this grass to warrant treatment. All of the other grasses ripen at about the same time, and since timothy is one of these and has an abundant pollen, treatment with timothy pollen seems to protect sufficiently against the other grass pollens. In the fall



hay fever season only ragweed needs to be considered; the dwarf or small variety north of Connecticut and both the small and giant south of Connecticut.

*The Central States.*—In Kentucky, Ohio, Indiana, Illinois and Wisconsin, blue grass, timothy grass and lambs quarters are important from May to September and the ragweeds and careless weed from July to August. In Chicago, blue grass and orchard grass cause most of the hay fever during the early summer and the ragweeds and lambs quarters in the fall. The spring season is of little importance.

*The Mississippi Valley States.*—All have similar seasons and similar pollens as stated above with the addition of Bermuda grass and Johnson grass. Throughout the States of Minnesota, Iowa, Mississippi, North Dakota, South Dakota, Nebraska and Kansas, blue grass, timothy grass, lambs quarters, ragweed, careless weed and sage brush are the most important causes of hay fever.

*Southern District.*—In Oklahoma the maples pollinate the latter part of February, the cottonwood tree in April, and both cause some hay fever. Bermuda grass pollinates from the middle of May until frost and is a contributing cause in one third of all hay fever cases. Water hemp is a very heavy pollen producer and is a very common cause of hay fever in Oklahoma and in the eastern and southern parts of Texas, Nebraska and the southern part of South Dakota, Iowa and Michigan. From the middle of August until the first of October the ragweeds are important causes of hay fever.

In Arizona and the southwest, the season of pollination begins the last of January and continues through November. Furthermore, after the annual rainfall there may be a different flora or different causative pollens from one year to the next. Rabbit bush and shad scale cause spring hay fever; Bermuda grass and June grass cause hay fever in the spring, summer and fall. The Amaranths, rather than the ragweeds, cause the fall hay fever. Outside of the irrigated districts the pollen seasons depend upon the annual rainfall. In the irrigated valleys there is a continuous hay fever season for nine months. Cottonwood pollen causes hay fever in February, the ash trees in March, Bermuda grass begins to pollinate early in April and continues for nine months. In the latter half of the

season the pigweeds and Amaranths cause hay fever and, as already stated, Bermuda grass is still in pollination. In southwestern Texas the cedar tree causes hay fever during December, January and February; Bermuda grass during April, May and June and again from the latter part of August to November. In northern Texas the grasses and ragweed pollen cause most of the hay fever.

*The Mountain States.*—In Colorado the cottonwood trees cause hay fever in May; blue grass and grama grass in May, June and July, and lambs quarters and the ragweeds from June to frost. In the region about Colorado Springs cottonwood trees cause early hay fever and Russian thistle, sage brush and ragweed the remainder of the summer. In Nevada, during April and May, ash, olive and black walnut trees cause hay fever from April to October. Johnson grass and Bermuda grass cause much hay fever and in addition, during July and August, rye grass. From July to October Russian thistle is most important and careless weed and red root are less important as causes of hay fever in the late summer. In Montana there is little spring hay fever from the trees; more hay fever in May and June from the grasses and 60 per cent of all cases have hay fever from July to frost and this is caused by Russian thistle, sage brush and poverty weeds.

Oregon is divided by the Cascade Mountains into two distinct areas as regards pollens. To the east of these mountains June grass pollinates in May and June, bunch grass, wheat and tall rye grass during June and July and in the late summer and fall Russian thistle pollinates from June to September. Sage brush pollinates from June to August and Atriplex from June to September. West of the Cascade Mountains are several river valleys and the pollen flora is varied. However, since 96 per cent of all hay fever patients in Oregon have the early or midsummer type of hay fever, which is caused by the grasses, enumeration of the various floras is of no interest. In Utah, during the spring season from April to June, a few patients have hay fever from shad scale. The summer season from mid-July to September is the most important in that 83 per cent of the patients have hay fever at this time. The principal cause of hay fever at this time is Russian thistle. In California the pollen flora is so varied in different districts

that it is not possible to give a detailed report. Black walnut, orchard grass, rye grass, June grass, Bermuda grass, red root, pigweed and mug wort are hay fever-causing plants which are common throughout the state. In the Sacramento and San Joaquin Valleys olive trees and Johnson grass are important. In the region about Los Angeles and Pasadena careless weed is important. About San Francisco Bay sage brush is important. In Southern California during January and February the pollens of black walnut, English walnut, live oak, scrub oak, cottonwood and cypress are prevalent. During March, April, May and June the various grasses pollinate and of these the most important are Bermuda grass, orchard grass, red top and fescue. Bermuda and ray grass pollinate practically throughout the year. During July, August, September, October and November, first the wild rye species, Johnson grass and the *Atriplexes*, then follows the western ragweed and cockle bur, and finally the *Artemisia* family.

*Foreign Countries.*—There seems to be no late summer or fall hay fever outside of North America and the chief cause of hay fever, namely, ragweed, is not known. In Argentina there is a tree season in early spring and a summer season due to the grasses, which pollinate during January and February. In England, France and Germany the chief causes of hay fever are the grasses and the season is similar to that in New England. In Spain there are two grass seasons; early spring and late summer, and two thirds of all cases are caused by the grass family. The olive tree also causes considerable hay fever in Spain.

*Collection of Pollen.*—Pick the flowers when they are just ready to shed the pollen, spread them upon sheets of smooth paper in a closed room and allow them to dry. Much pollen will be found free upon the paper. The dried anthers with the pollen inside or sticking to them can be separated from the pollen by grinding them slightly with a mortar and pestle in small amounts of carbon tetrachloride. The carbon tetrachloride with the suspended pollen is strained through cheesecloth to remove the gross fragments, and then it is allowed to fall upon smooth filter paper, while the carbon tetrachloride runs through into the flask. The same sheet of filter paper is used several times until a large amount of

## THE CURABILITY OF POLLEN HAY FEVER

pollen has collected. The filter paper is then allowed to dry and the pollen forms a cake. This dry pollen is scraped with care from the filter paper and put into a clean, tightly corked bottle, where it will keep indefinitely. Pollen collected in this way is quite free from dust, is uncontaminated by other pollens, and seems to be more or less sterilized by passage through carbon tetrachloride. Pollen can be purchased from reliable firms that deal in biological products but they must be of the species indigenous to the patient's environment.

**Preparation of Pollen Extract.**—There are many different ways of preparing pollen extracts for use in the diagnosis and treatment of hay fever, and all of them seem to give satisfactory results when used by the worker who devises them.

A method in general use is that of Clock, which is to extract the pure pollen grains in 66.6 per cent glycerol and 33.3 per cent saturated sodium chloride solution. Another method is that of Coca's; the dry pollens are treated with ether so that all the fats are removed, then the pollen is extracted with the following solution: sodium chloride 0.5 per cent, sodium borate in such concentration that 10 cc. of the final fluid contains about 3 cc. of tenth normal alcolide and carbolic acid is added in a final concentration of 0.4 per cent. Alles and Lohr extract the dry pollen grains with occasional shaking in a fluid containing glycerol, sodium dihydrogen phosphate and sodium hydrogen phosphate. This extract is isotonic with blood, has a hydrogen ion concentration within the limits of normal blood sera, seems to contain all of the salt and soluble active substances present in pollen grains, and is stable.

The method used by the writer is to extract 1 Gm. of pollen in 88 cc. of normal saline with frequent shaking for twenty-four hours; then 12 cc. of absolute alcohol is added to make a 12 per cent alcoholic saline solution and the extraction is carried on with occasional shaking for another twenty-four hours. To the extracting fluid carbolic acid is added to make a final 0.4 per cent. This alcoholic, sodium chloride, carbolic acid solution is used for further dilutions of the pollen extract.

**Methods of Testing for Pollen Sensitivity.**

*Cutaneous Test.*—A number of small cuts, not scratches, each about  $\frac{1}{8}$  inch long, are made on the flexor surface of the forearm. The cuts are made with a sharp scalpel, with an even pressure, so that they are deep enough to penetrate the skin without drawing blood. Sometimes in testing infants or small children the tests are made on the back. On each cut is placed a very small amount of the dry pollen to be tested. When all of the pollens have been applied to the cuts, a drop of tenth normal sodium hydroxide (4 Gm. NaOH to 100 cc. of distilled water) is added to dissolve and to admit of its rapid absorption. Great care should be used not to carry pollen from one cut to the next and not to contaminate the fluid. At the end of half an hour the pollens are washed off and the reactions read. A positive reaction consists of a white area or urticarial wheal, often irregular in shape and with outrunners or pseudopodia, surrounded very often by a flushed or rosy area.

*The Intradermal Test.*—This consists of the injection into the skin of minute amounts of pollen extract, usually 0.01 cc. It consists, essentially, of a parenteral injection into the body of a foreign protein. The technic is rather difficult, since the volumes to be injected must be exactly the same in the control as in the diagnostic tests, for accurate comparison of the size of the reactions. The intradermal test is so very sensitive that false reactions or pseudoreactions are a common occurrence. The tendency to multiple or group reaction to botanically related pollens, is common so that the intradermal method is sometimes unsatisfactory as an indication of the specific pollen which causes the hay fever symptoms. The most serious objection to the use of the intradermal test is the occurrence of severe local or constitutional reactions.

All plants belong to some biological family of which there are numerous members. Consequently, some plants are so closely related to each other that all members of that family will give a positive test whether cutaneous or intradermal, even though only one member may be the cause of hay fever. To illustrate this: a patient, who has hay fever in the fall of the year that is caused by ragweed pollen, will react more or less positively to daisy pollen, which is present in the air in midsummer, and which, because it is so heavy, it does not blow

about, does not cause hay fever. A patient who is sensitive to the grass family will react to the pollen of all grasses and to corn, which belongs to the grass family. Such a patient, however, would be tested for and treated by timothy pollen in the east, and Johnson grass and Bermuda grass in the south and west, and there is no necessity for treatment with corn pollen, which does not blow about to any extent. Therefore, it is necessary to test and treat the patient with only that particular pollen to which he is exposed.

Before treatment is instituted it is essential that the patient be tested with various strengths or dilutions of the particular pollen protein to which he may be exposed. The original pollen extract may be diluted so that when tests are done with various strengths or dilutions the degree of sensitivity of the patient may be established. When this is done it is usually found that the pollen which is the cause of hay fever gives a positive test in the greatest dilution or with the least amount; whereas other members of the pollen family, to which the patient is not exposed, require larger amounts of the pollen to give a positive test, and some members of the family may react very little with very large amounts.

**Preseasonal Treatment.**—Unless the patient is tested with graded amounts of the pollen protein, such as various strengths or dilutions it is not possible to know the initial dose for treatment or when to start treatment. Without these graded tests the first dose of treatment may be too large, thereby causing a distressing reaction, or the first few doses may be unnecessarily too weak to be of value. Furthermore, knowledge of the positiveness of the patient to various strength or dilutions of the pollen protein is an important guide in treatment. For example: a patient reacts as follows: 1: 100 is 4+, 1: 500 is 3+, 1: 1000 is 2+, 1: 5000 is 1+, 1: 10,000 is  $\pm$ , 1: 20,000 is doubtful, 1: 40,000 is 0. It is safe to begin treatment with 3 minims or 0.2 cc. of 1: 40,000. If no reaction occurs from this dose and none would be expected, the next dose would be 3 minims or 0.2 cc. of 1: 20,000, and no reaction would be expected. The third dose would be 3 minims or 0.2 cc. of 1: 10,000 and although no reaction would be expected it is known from the tests that from now on treatment should be slower and not increased so rapidly; therefore, the

fourth dose would be 5 minims or 0.3 cc. of 1: 10,000. The fifth dose would be 3 minims or 0.2 cc. of the 1: 5000 dilution; the sixth dose would be 5 minims or 0.3 cc. of 1: 5000. Since there is a greater jump from the 1: 5000 to the next dilutions of 1: 1000 than there was in the preceding dilutions, it is necessary to give two more doses of the 1: 5000, namely, 7 minims or 0.4 cc. and 9 minims or 0.6 cc. Although a mild reaction may follow the latter doses, a distressing reaction would not be expected. However, should one of these doses cause a large, red, hot, local reaction at the site of treatment or any constitutional reaction, the dose that was responsible should be repeated before proceeding with the schedule. Since the next dilution, namely, 1: 1000, caused quite a reaction in the tests, we are forewarned to proceed cautiously. Therefore, with this 1: 1000 dilution, in order to be as safe as possible, three doses are given, namely, 3, 4, and 5 minims or their equivalent in the metric system. With no reaction following these three doses, and none would be expected, it is then proper to give the 1: 500 dilution in doses of 3-4-5-6-7 minims or their equivalent in the metric system. This schedule calls for 16 treatments without any repetition. In 9 cases out of 10 an excellent result would be expected.

The above schedule is often varied to fit the degree of sensitivity of the individual patient, with consideration of the ability of the patient to tolerate an increase in the amount of pollen injected, as judged by the effect of each preceding treatment. Very sensitive patients, who require treatment with the 1:160,000 or even higher dilutions, are frequently unable to take the larger amounts of pollen extract dilutions before the time of onset of the symptoms, but they receive a great deal of benefit from treatment with the dilutions which they are able to tolerate. Less sensitive patients are sometimes treated with a 1: 100 dilution of the pollen extract in amounts of 0.1 cc. or 2 minims, 0.2 cc. or 3 minims, and 0.3 cc. or 5 minims. Since the best results are obtained when treatment is given at weekly intervals, and since 16 treatments are outlined, it is best to begin treatment sixteen weeks before the usual onset of hay fever symptoms. Treatment given at five-day intervals offers nearly as good results. Treatment that is given at more frequent intervals does not produce as satisfactory results.

Successful preseasonal treatment depends upon the following: (1) to start the course of treatment early enough to complete the schedule a week or ten days before the usual time of onset of the symptoms; (2) to test by the cutaneous method with the actual pollen extract dilutions which are to be injected in treatment; (3) to adjust the initial amount to the degree of sensitivity of the patient, *i. e.*, start with the dilution which gives no reaction, but is next higher to a dilution to which the patient gives a slight reaction; (4) to increase the amount or strength of the injections as rapidly as the patient can tolerate them with no more reaction than a slight and transient local irritation about the site of the injection (swelling less than the size of a fifty-cent piece, with surrounding flush, of less than twenty-four hours' duration); (5) to repeat any amount that causes any marked local or any systemic reaction; (6) to inject the material subcutaneously, not intradermally, intramuscularly, or intravenously.

**Coseasonal Treatment.**—This method of treatment differs from the preseasonal method only in that treatment is started just prior to or after the onset of hay fever. The results are not nearly as satisfactory as those obtained from the preseasonal method. Furthermore, it is hazardous because the patient is being exposed to pollen in the atmosphere at the time he receives treatment, and there is no way of estimating how much pollen the mucous membranes are absorbing at the time of treatment. In those cases where the patient is sensitive to several different species of pollens it is of some advantage to treat with some pollens coseasonally, provided the preseasonal treatment can be given with only a part of the pollens. If the patient applies for treatment after his hay fever has started and the season is a long one, it is well to give the coseasonal treatment a try; if it benefits, the patient is the gainer; if it fails, it can be stopped.

**Preseasonal Combined with Coseasonal Treatment.**—When a patient applies for treatment four to ten weeks before the usual onset of symptoms, a combination of the pre-seasonal and coseasonal treatment may be given. The treatment is carried out as outlined for preseasonal treatment up to the time the patient begins to have hay fever symptoms. From then on the increase in dosage is adjusted in accordance with



the condition and reactions of the patient. During the season the patient may not tolerate increased amounts of the pollen extract but may obtain much relief from repeated doses of a quantity that he can tolerate.

The results from the combination of preseasonal and coseasonal treatment are not as good as from the preseasonal treatment alone, but are much better than from the coseasonal treatment alone.

**Perennial Treatment.**—This method really consists of giving more or less preseasonal treatment, then continuing during the hay fever season with as much treatment as the patient will tolerate and after the hay fever season is finished and the time has arrived to again start the preseasonal treatment.

The aim of this method is, after a certain amount of immunity has been established, to hold or preserve as much of this immunity as possible until another course of preseasonal treatment can be started for the purpose of a further increase of immunity, etc. The advantage of this treatment over pre-seasonal treatment alone is that between courses of the latter there is a more or less decrease in immunity during the interval of no treatment. From the patients' point of view the inconvenience and expense of such a prolonged series of treatments may offset any advantages this method may have over the pre-seasonal method.

**Seasonal Results of Pollen Treatment.**—With the careful adjustment of treatment to each patient, as has been detailed by making tests with the same pollen dilutions that are to be injected in treatment and by using the proper pollens, preseasonal treatment offers much benefit to 85 per cent of cases. In districts where the pollen flora is not extensive, such as in New England, 98 per cent of patients are greatly benefited. Over a period of fifteen years the writer finds that the average results from his treatment is that 15 per cent of patients have no hay fever; 30 per cent have practically no hay fever; 40 per cent are at least 75 per cent improved; 10 per cent are 50 per cent improved, and the remaining 5 per cent are not benefited. In other districts where the pollen flora is more extensive, such as in Arizona, where Bermuda grass and June grass cause hay fever during the spring, sum-

mer and fall and in addition the amaranths cause fall hay fever, the results would not be quite as satisfactory because of the necessity of using several pollens in the treatment at the same time and because the grass season is so long.

From coseasonal treatment alone the results are not very good, but the combination of preseasonal and coseasonal treatment offers results that approximate those from preseasonal treatment. Perennial treatment gives equally good results.

Cutaneous tests with pollen dilutions at the end of a course of treatment are much less positive than at the beginning of treatment. But this greatly decreased sensitivity does not hold over completely until the next course of treatment is instituted. However, at the beginning of a second course of treatment, the cutaneous tests are as a rule much diminished over those which prevailed at the beginning of the preceding course of treatment. Therefore, with each course of treatment there is a gradual diminishing in the cutaneous tests and there is a gradual improvement in the symptomatic results of succeeding treatments.

**Permanent Results from Preseasonal Pollen Treatment.**—In my own experience with my own pollen extracts permanent relief has been obtained in one third of those so treated. Only a few patients have been permanently cured following one or two seasons of treatment and the majority of cures followed three, four, five and six successive preseasonal courses of treatment. If the number of those who were treated from three to six successful seasons were considered, the percentage of cures would be nearly 50 per cent. In fact, 55 per cent of all those treated four successive seasons, and 65 per cent of those treated five successive seasons have had permanent relief. About 5 per cent of the whole number have had treatment for seven or eight seasons and although they obtained complete relief from each season's treatment, their cutaneous reactions have not shown any permanent decrease and the few who have omitted a season's treatment at various times had considerable hay fever that season. Therefore, it would seem that this 5 per cent of the total would probably never be permanently cured. There are two guides or indices that tell when an apparent cure is reached and treatment may be safely omitted. One is, when the cutaneous reaction to the

causative pollen has become negative and the other is, that the pollen reaction must show a considerable decrease if not negative, and the patient should have had two seasons of complete relief from hay fever while under treatment.

About 20 per cent of those who have had permanent relief from pollen hay fever were never completely free from symptoms while under treatment. They were patients who had more or less symptoms throughout the year from causes and conditions other than pollens. This establishes the fact that pollen hay fever patients may have symptoms from causes other than pollen, that the pollen cause may be cured but there still may be more or less symptoms which must be explained on some other basis.

The positiveness of pollen tests in these cases usually diminishes with each succeeding course of treatment until the tests become negative or there is a very great reduction in the sensitivity. When this occurs it is logical and usually safe to stop treatment. Causes and conditions which produce symptoms, even though the pollen cause has been cured, will be discussed in succeeding paragraphs.

#### **Complications in the Treatment of Pollen Hay Fever.**

—In the complicated cases of pollen hay fever treatment is not as simple as in the pure pollen cases and it is this group of patients that perplexes the practitioner and the handling of these cases is best accomplished by the experienced or specialist. These complications may be perennial or seasonal.

*Perennial Complications.*—A mild vasomotorhinitis, a sensitive mucous membrane of the nose that is manifested only by sneezing and watery discharge, and the susceptibility to so-called "frequent" head colds, any of which conditions may be due to sensitization to some protein other than pollen, and more often due to a mild bacterial infection, may be present in a patient who has pollen hay fever. The patient may have become quite accustomed to the perennial condition and may seek relief only from the seasonal hay fever; therefore, a careful history is important. Occasionally a patient is slightly sensitive to some food protein or to an animal protein, not enough to cause symptoms throughout the year but during their hay fever season the combination of these with the pollen to which they are sensitive is sufficient to cause mild symp-

toms in treated cases. Similarly face powder, which is used more extensively in the warm months, may cause symptoms. Mechanical irritants such as soap, powders, dust, train smoke, gases, perfumes, etc., may cause little trouble throughout the year, but more trouble when the mucous membranes are already somewhat irritated by pollen. Abnormal conditions of the mucous membrane may permit aggravated symptoms when these membranes are irritated by pollen.

*Seasonal Complications.*—Since the cereals belong to the grass family, a patient who is sensitive to both the grass and late fall pollens, may have some hay fever in the fall from husking green corn; the corn pollen is present in the husks. Insect-pollinated flowers, when kept in the house as a bouquet, dry out, and their pollen may then blow about or be inhaled. If these plants belong to the same family as the ones to which the patient is sensitive, they may cause some irritation. Some patients are sensitive to certain foods which are eaten only during the summer and these may cause hay fever or in a treated case they cause brief attacks of sneezing and lacrimation following their ingestion. Ingestion of beers, wines, and hard liquors often is immediately followed by an attack of hay fever of a few hours' duration in a pollen-sensitized individual.

It is often difficult to differentiate between a summer head cold and an attack of hay fever, whether the patient is or is not sensitive to a pollen. Sudden changes in temperature provoke nasal secretion and fits of sneezing in many individuals, and those reactions may resemble the symptoms of pollen hay fever. In the spring and in the autumn, when the days are warm and the nights are cool and damp, many individuals, whether sensitive to pollens or not, will have an attack of sneezing and watery nose on arising in the morning and again in the evening until more clothing is put on. For the conditions mentioned in the paragraph, a vaccine often greatly benefits or relieves.

It is not uncommon to test patients who complain of hay fever at a time which corresponds more or less accurately to some pollen season, and find them negative to all proteins, including pollen proteins. A careful history, however, will often solve the problem. Usually such patients do not have con-

tinuous symptoms, but instead, a day or two of symptoms may alternate with a day or two of freedom. Their symptoms are frequently worse on cold, damp, rainy days when, of course, there is no pollen in the air, and they are much better or completely relieved on warm, sunny days, when there is abundant pollen. These are usually of bacterial cause and vaccines are indicated. Without tests and a careful history, the physician would suspect, and often would treat the patient with the pollens that were prevalent at that season with no benefit.

The odors of fragrant flowers, face powder perfumes, soap or any pungent odor, the inhalation of gases, dust, train smoke, burning leaves or cloth, etc., often irritate a mucous membrane that is already irritated by pollen and have no effect at any other season.

**Conclusion.**—It is evident that a careful history should be taken from all hay fever cases with especial attention to the time of year that they are effected and to other influences or complications. It is essential to know to what wind-blown pollens the patient is exposed; tests will tell to what pollens the patient is sensitive, but the physician must know to which the patient will be exposed. Before treatment is given tests should be made with different strengths or dilutions of the causative pollens. Such tests will help to select the proper pollen since it will react strongest, they will tell when to start treatment since the number of treatments will be defined by these tests and the tests are a guide to the different doses to be given. Treatment should be intensive with as few pollens as possible. It is not advisable to treat with a mixture of pollens from very closely related plants that pollinate at the same time because intensive treatment with one of them will protect against exposure to the group. Definite directions and a well advised schedule of treatments may have to be altered in any particular case; the schedule may call for too strong a dosage in one case or too weak in another. Such directions and schedules are a guide to proper treatment and if they are determined by previous tests they are usually satisfactory. Directions and schedules that are formulated without a previous test on the patient to be treated are apt to be valueless.

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### THE PRACTICAL MANAGEMENT OF CONGESTIVE FAILURE

CARDIAC failure of the congestive type is one of the most common problems encountered in medical practice. Although a familiar subject, it is none the less full of interest on account of the variety of its manifestations and of their response to treatment. To be sure, the main principles of treatment are well enough understood but their practical application to patients with congestive failure provides many opportunities for the display of resourcefulness on the part of the clinician. It is a condition where minor tactics often play a decisive rôle in the outcome and it is to these homely practical details that we shall chiefly devote our attention today. The discussion will be grouped around *general measures, drug therapy and mechanical measures.*

**General Measures.**—*Rest.*—In the treatment of severe grades of congestive failure, rest must mean a great deal more than mere confinement to bed. Its real meaning is best understood in terms of metabolism by saying that the metabolic rate should be maintained as close to the basal level as practicable. In order to achieve this, there must be a minimum of muscular activity, of mental and of digestive activity and an attendant strong enough to move the patient should be constantly available to spare him any unnecessary exertion. While acutely ill he must, of course, be fed, bathed and shaved and, during this stage, the bowels are best emptied by enema, preferably by the two-way enema or low colonic irrigation. The latter

possesses the advantage of not requiring the use of a bed pan, so that the patient does not have to be moved. The bed pan is a physical and mental hazard to the bed-ridden cardiac. For many it is less of a strain to be moved onto a commode beside the bed. The stools must be kept soft with cathartics so that there is no expulsive straining.

The optimum position of the cardiac patient in bed will depend upon the degree of orthopnea to which he is subject. A few with extreme orthopnea will be most comfortable in a chair. A new "cardiac bed" in which the foot lets down while the head comes up is a great comfort for these patients. In determining how long to keep a patient with congestive failure in bed, one has to bear in mind that the longer he remains in bed the more skeletal muscle tone he will lose and, with it, peripheral vascular tone. This will tend to increase the strain on the heart when he first gets up. For this reason and on account of the danger of hypostatic pneumonia, it is advisable to get aged patients sitting up in a chair just as soon as possible. For the same reason, gentle massage and passive exercises are worth-while procedures during convalescence.

Mental rest is also an important objective in the treatment of cardiac failure. If the condition is acute, the patient is apt to be the prey of anxious thoughts and disturbed sleep. Under these circumstances morphine is indicated as much for the comforting euphoria which it induces as for the reliability of its soporific effect. Later on, of course, the main dependence for sleep must be placed on less habit-forming drugs such as the barbiturates or chloral hydrate. Restless patients often feel better during the day if the "edge" is taken off by a mild sedative such as phenobarbital,  $\frac{1}{2}$  grain three times a day.

The sick room must be as restful and quiet as possible and kept at an even temperature. Visitors should be strictly limited and should be cautioned against allowing the patient to do much talking.

*Diet.*—The diet of a cardiac should consist essentially of concentrated low residue, high carbohydrate foods given in small amounts at frequent intervals. This accomplishes several purposes. It avoids undue strain on the heart from overloading the stomach, it reduces the amount of bowel residue

to be expelled, it furnishes glucose in readily available form to replenish exhausted glycogen stores in the myocardium, and it minimizes the stimulation of metabolism from specific dynamic action. In the critical stages the carbohydrate may be given in the form of concentrated dextrose solution intravenously. For oral use fruit drinks sweetened with glucose or lactose are employed. The Karell diet (800 cc. of milk per day) is useful on account of its simplicity and its low caloric content. As Master has shown, the basal metabolic rate of a cardiac patient may be lowered to as much as minus 30 by a low caloric diet. Easing the load on the heart in this way may prove useful in the treatment of obstinate cases of congestive failure.

The fluid intake must, of course, be rigidly restricted. Not more than a quart a day is a good general working rule. It is well to ration it out in small amounts at stated intervals during the day so that it will not all be squandered before noon. Salt also should be limited because of its action in binding water in the tissues. In most cases a restriction of salt to what has been put into the food in the kitchen will suffice, but an obstinate few will require a completely salt-free diet. The substitution of potassium chloride for sodium chloride as a table salt is worth while in patients with chronic edema. The potassium chloride will furnish almost as much savour without the water-binding effect of sodium chloride.

Oxygen therapy is indicated if cyanosis becomes marked. The oxygen tent or chamber is the method of choice. but if not available, the nasal catheter will usually prove satisfactory. The disadvantage of the nasal catheter method is not that it does not deliver oxygen in sufficient concentration to the nasopharynx but that it is apt to be uncomfortable for the patient. The chief sources of discomfort are insufficient saturation of the oxygen with moisture so that the patient's throat is burned, and the use of catheters which are too stiff. If due attention is paid to such details the patient will often experience a feeling of marked relief when oxygen is started and may drop off to sleep. Objectively there is usually an improvement in the color and the respiratory and pulse rates are slowed. Improvement in intraventricular conduction during oxygen administration has been demonstrated and suggests that the



efficient functioning of the myocardium itself may be enhanced by this procedure.

**Drug Therapy.**—*Digitalis*.—A word has already been said about the important place which the opiates and the sedatives occupy in the treatment of congestive failure. Of the specific cardiac drugs, digitalis, of course, still ranks foremost. Digitalis therapy has been somewhat confused by the myriads of proprietary preparations which have appeared on the market in recent years. These preparations vary widely in potency and a few still make unwarranted claims in regard to not causing "gastric irritation" and nausea. The nausea of course is due to an effect on the vomiting center and not to any local effect in the stomach. A digitalis preparation which will not produce nausea in large doses is not a potent preparation. Occasionally one encounters a patient who has been conditioned against digitalis by having been nauseated by it in the past. To such a patient the smell and taste of digitalis is nauseating and if they are to take it by mouth it must be given in the form of a coated pill. It is very seldom that one finds a person who is really sensitive to digitalis.

In determining the dosage of digitalis to be administered to a given patient the Eggleston formula of 1.5 grains (0.1 Gm.) of the powdered leaf or 15 minims (1 cc.) of the tincture for every 10 pounds of body weight is a useful guide. There is so much variation in individual tolerance to the drug that even if all preparations were of fixed potency, no formula for dosage could be more than a rough index. In general, the tolerance to digitalis is proportional to the total metabolism. For this reason, children, active ambulatory patients and patients with fever or hyperthyroidism require relatively larger doses—sometimes twice as much per unit of weight—as compared to the aged, the inactive bed ridden and those in whom a significant proportion of the weight is due to inert edema fluid. Since it is impossible to predict exactly how much a given case will tolerate it is well to approach the estimated total optimum dose gradually. For example, if it is desired to digitalize a 150 pound man in twenty-four hours, the estimated total dose would be  $\frac{1.5 \times 0}{10} \times 150 = 22.5$  grains. This would be divided up as follows:

	<i>Individual dose.</i>	<i>Total dose.</i>
Initial dose.....	9 grains	9 grains
Three hours.....	6 "	15 "
Six hours.....	3 "	18 "
Nine hours.....	1½ "	19½ "
Fifteen hours.....	1½ "	21 "
Twenty-one hours.....	1½ "	22½ "

Inquiry as to anorexia or nausea should be made before each dose is given and the drug discontinued at the first sign of toxicity. If no effect whatsoever is noted, it may be continued in doses of 1½ grains three times a day until an effect is produced. If the patient has had an uncertain but apparently inadequate amount of digitalis, he may likewise be given 1½ grains three times a day. This dosage is also useful in digitalizing ambulatory patients who are not under close supervision, as in the average person one week of it gives approximate digitalization. In regard to digitalis dosage the dictum of Withering published in 1785 still holds good. He wrote: "Let the medicine, therefore, be given in the doses, and at the intervals mentioned above; let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any one of these effects." Other indications for discontinuance of the drug are the appearance of yellow vision and very frequent extrasystoles or bigeminal rhythm.

The electrocardiogram may yield further information in regard to the effect of digitalis on a given patient. It may show, by a specific change in the contour of the T waves, plain indications of a drug effect long before toxic signs appear. It may also give evidences of toxic action not readily detectable by other means of examination (partial heart block, frequent extrasystoles or periods of complete heart block in auricular fibrillation). In children, however, the electrocardiogram may remain normal in the presence of digitalis poisoning.

Some of the drug houses, in order to assure the consumer of a potent product, now dispense their digitalis products in terms of cat units. The cat unit is approximately equal to 1½ grains (0.1 Gm.) of the digitalis leaf (U. S. P.) which is standardized in frog units. For convenience and precision of dosage the pill prepared from the whole leaf is very satisfactory for routine oral administration. Occasionally it is necessary to

administer the drug parenterally, the indication being more often gastric disturbances than the necessity for extreme haste in digitalization. It is here that some of the purified extracts of digitalis have a place. The most powerful of these is crystalline ouabain, which is one thousand times as potent as standard digitalis. One mm. of ouabain intravenously is the maximum dose in an adult and should be divided into at least two injections given one half an hour apart. Strophanthin is a related compound of approximately equal potency derived from another source. These powerful drugs must be used with greatest caution, particularly if there is any question as to the amount of digitalis the patient has had just previously. Satisfactory preparations are also available for intramuscular use. Rectal administration is less satisfactory because one is never sure exactly how much has been absorbed. Dosage is the same whichever way the drug is administered. The average daily maintenance dose of digitalis is  $1\frac{1}{2}$  grains but some individuals cannot take half this dose and others will require three times as much.

By far the best results from digitalis are to be expected in the group of patients suffering from auricular fibrillation with rapid ventricular rate. The chief benefit in these cases is the elimination of the premature, inefficient, ventricular contractions. No such dramatic results are seen in auricular fibrillation with slow ventricular rate or in normal rhythm. The contrast is indeed striking, but should not obscure the fact that digitalis is usually of definite, although limited value, in the latter group.

*Diuretics.*—The importance of diuresis *per se* in the management of congestive failure can not be too strongly emphasized. Edema is much more than an inert burden of water, for in many ways it acts as a vicious aggravating factor to increase the work of the heart. In the lungs it causes respiratory distress and brings about a lowered oxygen tension in the blood with all the resulting train of altered function in vital organs, including the myocardium. In a limb it has been shown to increase the minute circulating volume of blood, again throwing an extra burden on the heart. Its presence in the liver, the kidneys, the intestinal mucosa, indeed in the myocardium itself, interferes directly with the function of

those organs. Edema, therefore, is to be regarded as a harmful complication to be eliminated as promptly and as completely as possible.

Of the specific diuretics we need discuss only the two most important groups—the mercurials and the purines. The most satisfactory mercurial on the market today is salyrgan. This drug combines a powerful diuretic effect, with a minimum of toxicity. Being a mercury compound it is contraindicated in the presence of advanced kidney disease but appears to exert no deleterious effect on the normal kidney. I have had occasion to use it twice a week over a period of three years in a patient with congestive failure and a mild degree of arteriosclerotic nephritis without any aggravation of the renal condition. It possesses the advantage over the milder purine diuretics of greater reliability of action and—because it is given intravenously or intramuscularly—of not upsetting the stomach. The dose varies from  $\frac{1}{2}$  cc. in children to 2 cc. in adults. Preferably it is given intravenously, but if veins are not available it may be given intramuscularly in the deltoids. If it is deposited subcutaneously or in edematous tissue where absorption is slow a slough will result. A diuresis usually appears within a few hours and persists for twelve to twenty-four hours. The dose may be repeated after three days. The drug is more effective if the patient is mildly acidotic, so that if no diuresis follows the first injection, a course of ammonium salts should precede the second. These salts possess diuretic properties themselves. Ammonium nitrate is preferable to ammonium chloride because it is less irritating to the gastrointestinal tract. It is best given in  $7\frac{1}{2}$  grain (0.5 Gm.) enteric coated pills—three pills every three hours for 6 doses on the day before and on the day of the injection. With this adjuvant a hitherto ineffective mercurial will often prove active.

The purines possess distinctly less diuretic effect than the mercurials but they have the advantage that they can be taken by mouth. They are indicated in the milder cases where the mercurial has proved ineffective. Caffeine is the mildest diuretic of the purines and too weak to be of clinical importance. The most commonly employed are theobromine and theophyllin. The former is given in doses of  $7\frac{1}{2}$  grains (0.5 Gm.) of the pure alkaloid or 15 grains (1 Gm.) a day for

two or three days of theobromine sodium salicylate three times a day. Theophyllin is given in the same manner in doses of 4 grains (0.25 Gm.) three times a day. Both of these drugs have the disadvantage of frequently causing gastric irritation, nausea and vomiting. The purines may be used in conjunction with the mercurials to obtain an enhanced effect. A new preparation called "mercururin," which combines the two in one ampule has proved to be a very powerful diuretic—the two drugs seeming to have an additive effect.

**Mechanical Measures.**—*Venesection.*—Venesection is indicated if the venous pressure is high, as evidenced by engorged neck veins, or if there is acute pulmonary edema. If there is no anemia from 400 to 600 cc. of blood should be withdrawn.

*Tapping.*—Abdominal paracentesis is worth while if the ascites is considerable in amount (more than three liters) and may be followed by a sustained diuresis. Thoracentesis is justified if the amount of pleural fluid is sufficient to embarrass respiration. Removal of subcutaneous fluid by means of Southey tubes is useful in obstinate cases.

*Surgical Measures.*—In the last few years total thyroidectomy has been advocated in the treatment of certain obstinate cases of congestive failure. The procedure is radical and technically difficult. It requires the closest sort of organized teamwork between internist, surgeon and nursing staff. The patients must be picked with care, the ones most suitable for the operation being those who are edema-free in bed but who can not get up without developing congestive failure. Under ideal conditions, a fair proportion of such cases will be improved by total thyroidectomy. It is not likely that it will be frequently resorted to.

The proper management of a case of congestive failure involves quantitative measurements of the effectiveness of the various procedures employed. The best rough index is a chart of the daily fluid intake and output. When the patient can be moved a weight chart is an invaluable check. The rapidity of weight loss in diuresis is sometimes astounding, reaching as much as 10 pounds in a day. The chart may also demonstrate the loss of edema "hidden" in the tissues which gave no physical signs of its presence.

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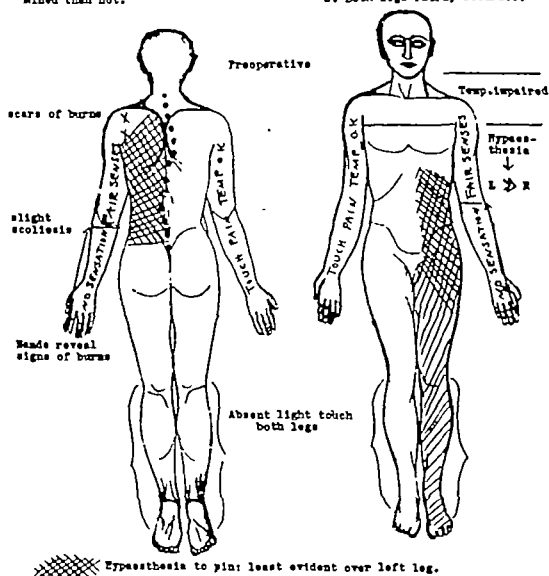
### SYRINGOMYELIA—DIAGNOSIS AND TREATMENT

**Case Reports.—Case I.**—A housewife of forty-eight was admitted to the Massachusetts General Hospital and gave the following history: about four years previously, she had stepped off a slowly moving train, and had felt a slight snap in her neck, and pain and tingling radiating down both arms. She

#331681, E. P., Massachusetts General Hospital — 4  
POSTERIOR: ANTERIOR:

1. Temp. impaired roughly over same area as pain (slope downwards @ iliac crest) Cold better determined than hot.

1. Whole left side Temp.+++ impaired (from jaw down)
2. Rt. side: some mistakes
3. Both legs fairly accurate.



Total astereognosis and loss of position sense in hands. Marked past pointing. Fomberg positive. But position toes accurate.

Fig. 173.—Case I. Distribution of motor and sensory changes.

had had similar sensations occasionally in the legs also. For about a year before admission there had been complete loss of the sensation of pain in the right arm, so that she had frequently burned herself. More recently, the sense of touch and position sense had been impaired in the arms, and she had become slightly unsteady on her feet.

Neurologic examination confirmed her subjective complaints (Fig. 173). There was definite atrophy of the shoulder girdle. All deep reflexes were exaggerated on the right, and the left Babinski was equivocal.

x-Rays of the spine showed a forward displacement of the fourth cervical vertebra. Lumbar puncture showed normal dynamics and the fluid was normal except that the protein was increased to 58 mg. Iodized oil injected into the cistern could be seen to pass the cervical enlargement in a thin stream.

A cervical laminectomy was performed. The entire cervical cord was found to be reduced to a thin-walled sac filled with spinal fluid which had evidently caused an atrophy of the walls of the canal by pressure and so had permitted a pathological fracture. The sac was incised along the midline posteriorly over a distance of about 3 cm. opposite the fifth vertebra. It was lined with glistening ependyma, and the cavity evidently communicated with the fourth ventricle.

The patient made a good operative recovery, and was relieved of pain. Her arms improved, and she was able to get about. In the course of a few months, the weakness of the legs recurred and progressed in spite of x-ray treatments, so that the patient was helpless when last seen a year after operation.

*Case II.*—A mechanic of thirty-two was admitted to the Massachusetts General Hospital on account of a "hammer" deformity of the left middle finger. A plastic operation on the tendons was contemplated, but neurological examination showed a characteristic "dissociated" sensory loss, scoliosis and facial asymmetry. The patient was slightly ataxic, and it was learned that the scoliosis and unsteadiness had been present since infancy. This was before the days of either x-ray treatment or operation for syringomyelia, and all that could be done was to amputate the last phalanx of the affected finger, which was in the patient's way.

*Case III.*—A man of fifty-five was admitted to the Boston City Hospital following an attack of faintness. He had lost consciousness without obvious cause four times during the previous two and a half years. He had been having pain in both arms for five years, and some tingling in the left hand for a year and a half. He had lost much weight. There was atrophy of the deltoids and of the hands, especially the left. The pain was, at times, severe enough to require morphine. There was a Horner's syndrome. All modes of sensation were impaired in the left hand, but only pain and temperature in the right. There were exaggerated reflexes, a Babinski sign, and loss of position sense in the left foot. Lumbar puncture showed a partial block and increased protein.

Cervical laminectomy revealed two fusiform enlargements of the cord, one at C<sub>4</sub> and the other at C<sub>6</sub>. Both were opened; the lower one contained about 30 cc. of xanthochromic fluid, the upper was solid. The walls were dark and rough. Following operation the pain was less severe, but there were no objective changes. The patient's symptoms gradually progressed and he died fourteen months later.

*Case IV.*—A man of twenty-four was admitted to the Boston City Hospital complaining of weakness, stiffness and numbness of the right leg gradually increasing for three years. From seven to nineteen years of age, he had had attacks of unconsciousness with crude visual hallucinations. About a year before admission, his right arm also became weak and numb. Vision had

always been poor in the right eye. Examination showed facial asymmetry (Fig. 174), scoliosis, scars of painless burns on the fingers (Fig. 175), and

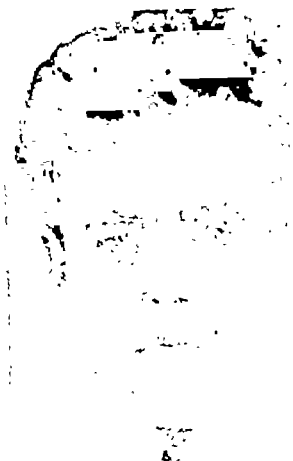


Fig. 174.—Case IV. Facies.

atrophy and fibrillation of various muscle groups of the shoulders and arms. There was bilateral clonus, Babinski's sign, and ataxia of the legs.

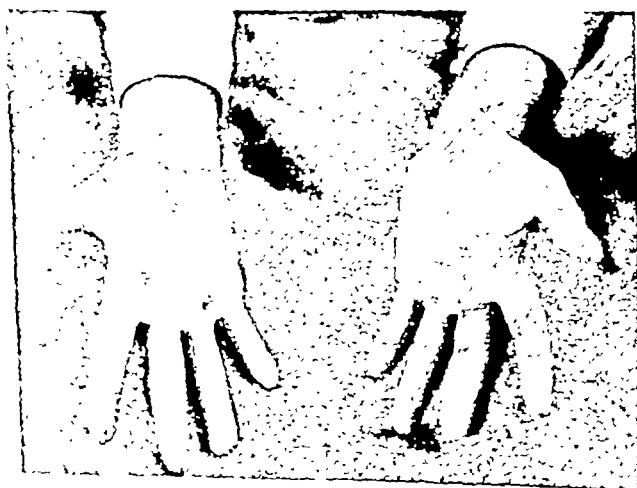


Fig. 175 Case IV. Painless burn of right hand, atrophy of hypothenar eminence.

There was a slight optic atrophy and a bilateral paracentral scotoma. Several lumbar punctures were performed, one of which showed 9 lymphocytes, another a protein of 83.



Several x-ray treatments were given, but the symptoms became worse rather than better. Finally, laminectomy was resorted to, and this disclosed an enormous cavity occupying the entire cervical cord, filled with spinal fluid. It was incised over a length of about 15 cm. The lining was a glistening white, and the walls nowhere more than 2 mm. in thickness. The cavity appeared to communicate with the fourth ventricle. The patient made a striking improvement after operation; not only did the sensory signs regress, but motor power was greatly improved, so that the patient could use his hands, walk long distances, and drive an automobile. The operation is now four years ago; the symptoms have very gradually returned, but have not yet reached their original severity.

*Case V.*—A man of twenty-eight entered the Boston City Hospital with the complaint that for three months his gait had been unsteady, especially at night. He also had a sense of coldness in the left arm and leg. Examination revealed asymmetry of the face, scoliosis, huskiness of the voice, and nystagmus in all directions. There was a loss of pain and temperature sense over the left side of the face, and also over the first four cervical and first and second sacral segments on both sides, without disturbance of sensation of touch. There was slight atrophy of left thenar muscles, and all deep reflexes were increased. The Babinski reflex was positive on both sides. Vibration and position sense was impaired in both feet, and there was an astereognosis of the left hand. Lumbar puncture showed normal dynamics and negative findings except for a protein of 58.

The patient was given x-ray treatment over the entire spine. In three months there was definite improvement, and he returned to work.

**The Diagnosis.**—These cases, picked almost at random, may serve to indicate the fact that syringomyelia does not by any means present the stereotyped clinical picture which most textbooks describe. To be sure, a "dissociated" sensory loss in the arms and some atrophy of the muscles of the hand is the rule. Indeed, the symptom of painless burns from cigarettes (among women, flatirons and stoves used to be equally common agents) is practically pathognomonic. But the standard teaching that injury to the long tracts is rare, should be abandoned. Some degree of spasticity, ataxia or loss of vibration sense is extremely common, and may be the presenting symptom. Pain in the arms is also often encountered. Atrophy of the muscles of the tongue or face with fibrillation has, of course, long been recognized, and so has the presence of nystagmus, but the frequency of their occurrence has been underrated. The explanation usually given is that the cavity extends into the medulla, but it seems probable that involvement of the cervical cord alone may suffice to produce it. A Horner's syndrome may occur.

Two somatic manifestations are of importance, first because they are almost constantly present, second because they may be immediately evident on inspection, and third, because of their possible significance in the interpretation of the nature and course of the pathologic changes. They are facial asymmetry and scoliosis. The facies may be strikingly similar from case to case (Figs. 175-177). Typically, the face is thin, the chin sharp, and the nose slightly out of line with the chin. One cheek is ordinarily more hollow than the other. The "bite" may be crooked. Pimples are common. Whether this facies actually is a "family resemblance" is an open question,



Figs. 176, 177.—Facies of two other patients, whose cases are not reported here. Notice "family resemblance"; rather long face, sunken cheeks, deep nasolabial fold, various slight asymmetries.

since we shall see below that the tendency to the disease is doubtless hereditary. It is perhaps more likely that both this and the scoliosis are the result of muscular imbalance, in turn dependent upon involvement of the grey matter. The fact that these manifestations may often be traced back to early childhood—as indeed the ataxia and some other symptoms may also be—is evidence that the underlying pathologic change is congenital.

Little emphasis has been placed upon *cerebral* symptoms, which have, however, been observed in so many cases that they can scarcely be dismissed as a coincidence. Syncope and

convulsions are the commonest, but others have been reported. It has seemed to me that a dependent, self-pitying attitude, sometimes combined with emotional instability and a tendency to blame others, was of frequent occurrence, but possibly this is merely a reaction to an affliction which is often progressive and crippling, and may occur in adolescence.

Visual symptoms are also encountered. Optic atrophy with enlarged blind spots is the only type I have observed personally, but papilledema has been reported. The possibility of confusion with multiple sclerosis and syphilis is obvious.

**Alterations Produced in the Spinal Fluid.**—The following data are summarized from the book "*The Cerebrospinal Fluid*," now in the course of preparation by Dr. H. H. Merritt, by his kind permission: in a group of fluids from 31 cases of syringomyelia, the pressure was over 200 cm. of water in 7 instances, for an unknown reason. In 2 cases, a subarachnoid block was demonstrated. In almost half the cases (including these two) the protein was higher than the normal upper limit of 46 mg. Occasionally a slight increase in cells was found. On the whole, therefore, examination of the spinal fluid is of little aid in the differential diagnosis from multiple sclerosis and cord tumor.

**Etiology.**—It has long been suspected, although on rather scanty evidence, that syringomyelia is the result of a hereditary defect. The disease may occur in association with other congenital defects and has been reported in two members of the same family. The observations of Ostertag,<sup>1</sup> that a similar condition exists as a recessive Mendelian trait in some strains of rabbits, lend a new weight to the theory. In these animals the lesions may vary from microscopic size to cysts which cause complete paralysis. In human beings also lesions of typical histology but too small to cause symptoms are a fairly common postmortem finding, usually in association with other neurologic diseases, for the spinal cord is seldom examined in subjects who have had no symptoms. It has been seen in this laboratory in association with spinal syphilis and myelomalacia, and has been reported with multiple sclerosis<sup>2</sup> and acromegaly.<sup>3</sup>

Alternative theories are that the cyst is the result of an as-

ascending neuritis or of a spontaneous hematomyelia dissecting up and down the gray matter. The fact the symptoms may be of insidious onset in childhood, and may progress irregularly or even regress, renders both improbable, as does the histology of the lesion. The cases in which an abscess of a finger has produced an ascending lymphangitis, and the signs of syringomyelia have then been discovered, may perhaps equally well be interpreted as instances of the increased danger of trauma and infection when the sensation of pain is absent from its sentry post. Hemorrhage into the gray matter may occur, and local pressure on the cord (as from a tumor) may cause necrosis chiefly in the gray matter, but in neither instance is a progressive process initiated. The symptoms of syringomyelia may often be first noticed, and possibly made worse, by injury, but close inquiry will almost always elicit evidence that the disease dates back to childhood.

**Pathology.**—The lesion usually described is one which begins in the gray matter of the cervical cord, and gradually spreads upward and downward. The fibers carrying the sensations of pain and temperature are usually involved more than any other group, either in the commissure or in the posterior horn. It is doubtless for this reason that the sensory loss may be greater on one side than on the other. The fibers subserving the sensations of position, vibration and (probably) touch run directly from the posterior root ganglion into the posterior column without a synapse, and are, therefore, less often injured, but they too may suffer. An irregular invasion of the anterior horns accounts for the muscular atrophy. The process is practically always most intense in the cervical region, but may spread up to the pons and down to the lumbar enlargement. The gray matter is chiefly involved, but the white matter may be injured also, perhaps in part by pressure.

It is usually stated that in true syringomyelia the cavity is distinct from the central canal and fourth ventricle, and contains a yellow fluid. If the cavity communicates with the subarachnoid spaces, the condition may be designated as hydromyelia, and it is often implied that this is a relatively benign condition. The experience gained by surgical interventions makes it appear probable that there is no real distinction between the two. In only one of my own cases has

the cavity contained xanthochromic material, rich in protein. In the six others, it contained spinal fluid, and evidently connected with the fourth ventricle. There was, however, no particular difference in the manifestations or clinical course of the disease in the two groups respectively, in my own cases, and in others in the literature. Usually the cavity is lined with a glistening white ependyma if it contains spinal fluid, and with a rough gray or brown glial growth if it is discrete. In one of my cases, both coexisted. The cysts containing spinal are usually the larger ones, and as in the first case reported above, may actually distend the cervical canal. It is no wonder that pain is produced by pressure on posterior roots. One would expect that the Queckenstedt test would more often show a block. It is probable that the fluid wave may be transmitted through the thin sac wall.

Histologically, the new formed tissue is found to be composed of fibrous astrocytes. There is usually little evidence of active proliferation; few nuclei lie in the thick feltwork of fibers. Vessels are rare. Occasional accumulations of blood pigment occur. No real inflammatory lesions are seen in the cord, but a mild meningoencephalitis over the brain has been reported. So has hydrocephalus.

The gliotic tissue may undergo a gliomatous degeneration. *At least, this is the current interpretation. It is possible that central tumors, and perhaps other processes, may produce cavities in the gray matter which are entirely secondary and not progressive. Further study is needed to settle this point.*

**Treatment by x-Ray.**—In every case, as soon as the diagnosis is made, roentgen radiation should be administered. It appears to be more effective early in the disease than later, and perhaps more should be expected of it as a preventive than as a curative measure. It is not universally effective. Improvement has been obtained in about 60 per cent of the cases reported in several series, but my own experience has not been as favorable. Some cases are definitely made worse by radiation. There is further the danger that excessive treatment will produce changes in the skin which may render subsequent operation difficult. It is, however, always worth trying, and may even be used as a diagnostic measure, for no other condition likely to be confused with syringomyelia is

likely to be affected favorably. Multiple sclerosis, for example, is distinctly aggravated.

**Operative Treatment.**—Atypical instances of syringomyelia may easily be mistaken for cord tumor, and doubtless many isolated cases have been operated upon since the early days of spinal surgery. The first surgeon bold enough to recommend opening the sac was Elsberg,<sup>4</sup> as far as I have been able to learn. A few subsequent operations are recorded, but the procedure remained a novelty until Poussepp reported two successful cases before the International Congress of Neurology in Paris in 1925.<sup>5</sup> Since then a large number of similar operations have been reported, the majority of them

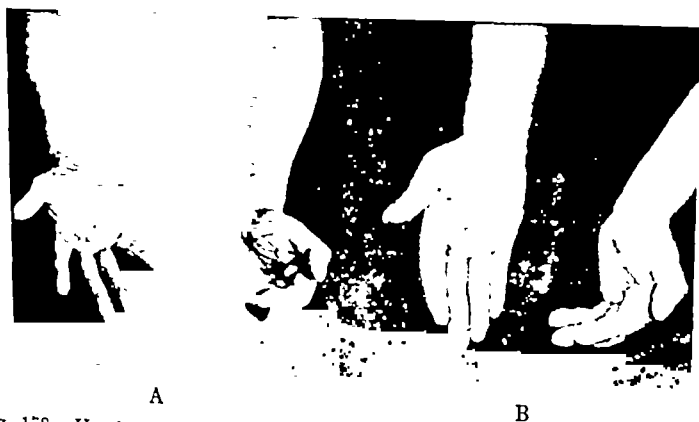


Fig. 178.—Hands of a patient with syringomyelia (not reported here) to show contractures. *A*, Before operation; *B*, after operation.

from Russia, where the disease appears to be unusually common.<sup>6</sup>

In general, the reports have been favorable. Most striking, both in the literature and in my own cases, has been the decrease of analgesia and anesthesia, and “before and after” charts have been frequently used as evidence of the efficacy of the procedure. Unfortunately, it is seldom the sensory disturbances which drive the patient to seek relief. The motor weakness in the hands and the injury to long tracts are less regularly improved, but sometimes definite benefit is demonstrable (Fig. 178). It is difficult to form an estimate of the proportion of favorable results from the literature, for evi-

dently successes tend to be reported in greater numbers than failures. In the 7 cases which I have observed personally, substantial improvement was observed in 4, although in all of them there has been some progress of symptoms since operation. In two others a decrease of the band of analgesia resulted, which looked well in the patients' record, but did not materially improve their ability to help themselves. Juzelevskij, who reported the largest series on record, gives somewhat similar statistics; 16 out of 22 cases were improved.<sup>7</sup>

On the other hand, the operation has not proved as dangerous in my experience as it is sometimes alleged to be. There have been no deaths, and no separation of the wound edges, which has frequently been recorded. One patient suffered a slight increase in the ataxia of one hand; otherwise, the postoperative condition has been no worse when it has been no better than that before operation.

The question has often been raised—does the opening in the sac close again? Recurrence of symptoms has taken place in several instances, and in a case reported by Frazier<sup>8</sup> the cyst had reformed. To avoid reaccumulation of fluid, it has been suggested that a drain of fascia or rubber be introduced into the drainage opening. From the pathological point of view, this would seem ill advised. A foreign body in contact with nervous tissue invariably becomes encapsulated in a mesodermal scar, which is exactly what one would wish to avoid. The problem is better met, it seems to me, by making the incision the entire length of the sac, or at least as long as the laminectomy allows. In the majority of instances, the edges will then gape apart and collapse into contact with the floor of the cyst. Whether adhesions will form, and whether the pia will obligingly regenerate to form a false passage from the lumen to the surface, must be left to future observation to decide. It would seem *a priori* unlikely, but some cases remain improved years after the operation. This brings up two minor technical points. The first is, where should the sac be opened? Poussepp suggests through the posterior horn of one side. My own policy has been to incise where the sac is thinnest, but usually in the midline, and this has not led to noticeable ataxia of the legs. When a long incision (of several centimeters) is made, bleeding may be troublesome, as the

posterior spinal vessels are too small to clip or tie successfully and too intimately attached to the cord to coagulate as they lie. If, however, they are gently raised on a dural hook, a light cutting current may be used to seal them without injury to nervous tissue. Collateral circulation is sufficiently rich to make up for any loss of blood supply.

**Indications for Operation.**—Weighing all of the considerations which have been enumerated, when should we recommend operative treatment? There is evidence that operation does not permanently halt the progress of the disease, and closure of the drainage opening is particularly to be feared if the sac is small. It is, therefore, not to be advised as a measure of prevention, which x-ray treatment appears sometimes to be. Radiation should be given a trial first, therefore, probably in all cases.

*Pain* is usually an indication for operation. It is seldom relieved by x-ray treatment, but usually yields to relief of tension within the sac. As pain is an important symptom of syringomyelia, the indication is an important one.

*Spinal block*, if it occurs, should probably prompt an operation. If there is an obstruction to the flow of fluid, the walls of the sac must inevitably be subjected to pressure, and this in turn is likely to be responsible for at least some of the symptoms. An increase in the spinal fluid protein is to be taken as presumptive evidence of block.

Finally, in many cases *economic disability* is a situation which justifies the pursuit of even remote chances of benefit. It is in this group of cases that the most marked and most gratifying improvement is obtained, and it is fair to hold such a possibility open even to extensively crippled patients.

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## CLINIC OF DR. STANLEY COBB

### MASSACHUSETTS GENERAL HOSPITAL

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#### CONCERNING FITS\*

If a patient greets you in your office with the complaint, "I have frequent headache," your mind runs rapidly over a list of possible causes, a shorter or longer list according to the extent of your experience. Many are rapidly eliminated as impossible or improbable in this patient. Nevertheless, days of study will be spent before the list of possibilities is cut down to a workable few. But if a patient greets you with, "I have fits, doctor," often your mind is filled with a vague concept of a "disease" called "epilepsy": inherited, deteriorating and hopeless. Such a concept frequently inhibits further intelligent research into the etiology of a particular case.

It is my contention that epilepsy is a simple, fundamental manifestation of nervous disintegration. "Disintegration" means here the loss of more or less of the functional harmony of the central nervous system. Integration is the main function of the central nervous system; it is the process of building up useful behavior patterns out of the many and varied stimuli that reach the cord and brain; physiologically it works by summation, facilitation, inhibition, long circuiting and co-ordination. The essence of the process is delay of incoming stimuli to allow for association and for reaction conditioned by past experience. Now this integration may be interfered with by physical or chemical injury to nerve cells, or by conditions which alter nerve function. Because I believe that a condition of interference with integration is essential to the production of fits, and because the interfering conditions are many and diverse, I believe that epilepsy cannot be called a disease.

\* Read at the meeting of the Suffolk District Medical Society, March 28, 1935, Massachusetts General Hospital.

To illustrate this I have made a chart (Fig. 179\*) enumerating 60 conditions associated with convulsions in man, some rare, some common. These 60 I have tried to explain on one or another physiological basis, and for this purpose have

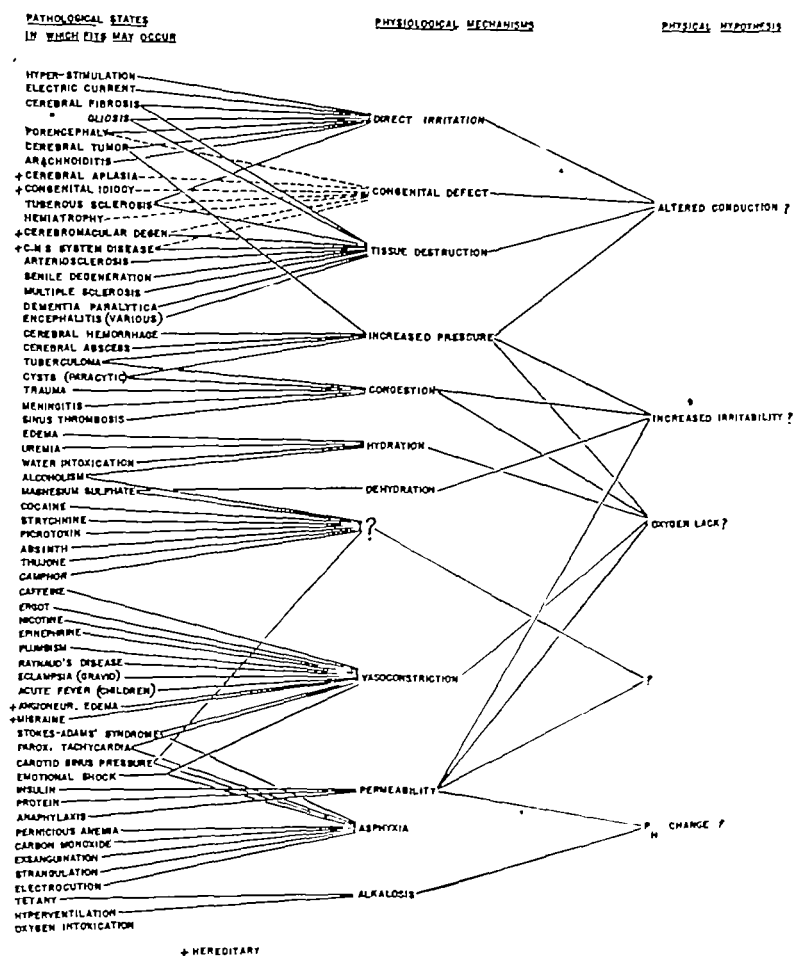


Fig. 179.

joined them by lines to 12 possible physiological mechanisms which have gone beyond normal limits and become pathological processes. These relationships are admittedly speculative.

\* A similar chart was published by me four years ago in the Arch. Neurol. and Psychiat., 27: 1245, 1932. The present chart is a revised and enlarged edition.

For a few there is good evidence; for others very little. Even more speculative are the four "physical hypotheses" which make up the last column; the most reliable symbol here is probably the large question mark! But there is no use in gathering data if they are not classified, analyzed and thought about. So the speculation is justified that altered conduction of the nerve impulses, increased irritability of the nerve cells, oxygen lack of the nerve cells, or change in acid-base equilibrium are probably important factors in many convulsions.

For the first two hypotheses we have the recent work of Gibbs, Davis and Lennox<sup>1, 2</sup> which shows by means of beautiful electro-encephalograms that epileptic seizures are accompanied by a change in the cerebral electrical potentials; this is recorded as a wave that has an apparently significant shape. Oxygen lack seems important because so many of the 12 physiological mechanisms may give rise to anoxemia, and because clinically, interference with circulation seems to be one of the surest methods of inducing loss of consciousness and convulsions. Acid-base balance may be important, but the evidence for it at present is based on a few observations on the blood of epileptics before attacks where there was a change toward the alkaline side, on the analogy with tetany, and on the occasional precipitation of seizures in epileptics by hyperventilation.

The inheritance of epilepsy is too much emphasized by physicians. Although the evidence supporting my opinion is far from complete, I believe that most convulsions are associated with acquired abnormality of the nervous system<sup>3</sup> and the acquired character cannot be inherited. On the other hand an injury to the brain may precipitate, and cause to become overt, a latent hereditary tendency to convulsions. The evidence for this is the observation that among the relatives of "traumatic epileptics" the incidence of epilepsy is about six times as high as among the general population, although it is only 60 per cent of the incidence among relatives of "idiopathic epileptics."<sup>4</sup>

In the list (Fig. 179) trauma and birth injury (causing fibrosis, gliosis, porencephaly, etc.), meningitis, encephalitis, and tumor, are the more important clinical causes. Only six (marked +) of the causes listed are known to be inheritable,

and these, except for cerebral aplasia<sup>5</sup> are rare. Hardly ever is epilepsy inherited as a syndrome without the inheritance of other associated neurological disorders. For example, feeble-mindedness due to lack of cerebral development may be found to run in a family. That the patients also have fits is explained by the aplasia and neurological short circuiting; it is an associated symptom. Yet because the fit is dramatic the whole picture is called "epilepsy." Other inherited nervous diseases that may be accompanied by fits are tuberous sclerosis, Friedrich's ataxia, and cerebromacular degeneration. But these are so rare as to be numerically unimportant. On the whole probably less than 8 per cent of epileptics show an inherited factor as judged by a history of epilepsy in a relative. Epileptic individuals who do have epileptic close relatives should be advised against having children. The remaining 92 per cent cannot reasonably be advised against marriage (if they can find mates). More epileptics come from families burdened with migraine than from epileptic ancestors, and the taint is often carried latent in a "normal" person. Therefore, the idea of effectively eliminating epilepsy by sterilization and "eugenics" is preposterous.<sup>6, 7</sup> Given laboratory control and thousands of generations it could be done.

Epilepsy means merely "seizure," a vague term at best, but it is usually understood to signify *sudden, recurrent changes in consciousness, often preceded by a sensory warning (aura) and often followed by motor discharge through the muscles (convulsion)*. Penfield and Gage<sup>8</sup> in an admirable paper on "Cerebral Localization of Epileptic Manifestations" say that under the heading of fits may be listed (besides convulsions) paresthesia, hallucinations of sight, visceral sensations, and autonomic phenomena. The list is so broad that there can be nothing typical about an epileptic fit, the essential being that *it is a disturbance of consciousness, overwhelms the victim suddenly and usually recurs in any one victim in a rather stereotyped pattern, or patterns*. In other words, each epileptic patient is likely to have his own special form of fit and to repeat it. He may have two or three which alternate; for example, it is common to have major seizures (grand mal) of one type interspersed with more frequent minor seizures (petit mal) perhaps resembling only the aura of the grand mal.

Thus it is difficult to differentiate epilepsy from other recurrent symptoms such as fainting (syncope), migraine (sick headache) and myoclonia. Syncope is often accompanied by a few convulsive jerks; migraine may have an aura and may begin entirely in the sensory sphere, but may change over into motor manifestations that anyone would call "epileptic." Moreover, fibrillary contractions, tremor, myoclonia, chorea, athetosis and convulsion form a series of muscular expressions of central nervous disorder that cannot be arbitrarily divided into those that are "seizures" and those that are not. One can talk of an attack, spell or fit of any one of them. But one talks of *epilepsy* only when there are *recurrent, rather similar attacks of disturbance of consciousness*.

Fits of a rudimentary sort may be elicited in the spinal cord; syncope and vasovagal attacks may be bulbar in origin; the diencephalon may discharge explosively giving rise to vasomotor, sudomotor and cardiac symptoms; and the forebrain with its many subdivisions gives rise to various sorts of seizures. Most attention has been directed to the cerebral cortex as the locus from which epilepsy usually arises. The conception is that a lesion in or near gray matter makes this gray matter more irritable than normal, lowers its threshold so that sudden, or slowly built up stimuli may cause a violent, disorderly neuronal discharge that we call a fit. The lesions may sometimes be actively irritating, as in the case of bleeding vessels, acute infections, growing tumors, or contracting scars. More often the lesion is more static, and seems by its mere contiguity to reduce the threshold of irritability of the adjacent gray matter; *e. g.*, old areas of fibrosis and gliosis following injury, slowly growing tumors, cysts of softening, and arachnoiditis. In the cerebral cortex this conception seems to hold true; much evidence has been accumulated by neurologists, surgeons and pathologists that focal lesions act as the starting point from which unbridled impulses spread to cause fits. They can only cause fits if they spread into comparatively normal tissue, for the neuronal discharge must be an exaggerated and explosive one that could not come from a badly damaged nerve cell. The wild impulses are excessive and disorganized, but in causing seizures they are probably acting through comparatively normal tissue.<sup>17</sup>

The evidence for this is extensive and well substantiated by operations on the brains of conscious patients. In the first place careful clinical histories have been compared with operative findings. Still more interesting are the results of electrical stimulation of the exposed brain in conscious patients. In normal animals convulsions may be brought on by excessive electrical stimulation of certain parts of the cerebral cortex, beyond the point of physiological response. Exploring the human cortex with an electrode at operation has located not only the motor area, where special movements are represented in the precentral gyrus, but areas from which synergic movements of the opposite side may be elicited, and movements of the head and eyes toward the opposite side. This particular movement has been elicited from several locations: area 6a in the frontal lobe, near the periphery of the occipital cortex, near the superior temporal, marginal and superior parietal gyri. It is interesting that this coordinated movement of the head and eyes turning to the side opposite the lesion is probably the commonest type of onset of a convulsion. Such movements may be precipitated by electrical stimulation of the cerebral cortex of an epileptic patient, and may lead to a spread of the motor spasm to other muscle groups with unconsciousness and general convulsion, just as in a spontaneous seizure. In fact, exploratory electrical stimulation may locate low-threshold "trigger points" at which the patient's typical attack may be set off.

When such a point is near the motor area (precentral gyrus or central sulcus) the attack begins *without aura*, the appropriate muscle group begins to twitch convulsively and then the convulsion spreads in an orderly way to other muscles. This *march* is observed by the patient and he *does not lose consciousness* until fairly late in the attack if at all. When the trigger point is in the postcentral (sensory areas) the attack usually begins with a localized numbness or tingling in a hand or foot, this spreads and focal motor phenomena appear usually simultaneously in both arm and leg, with less of the element of progressive march. In the occipital area the warning for the attack may be crude *lights*, red, blue or white followed by loss of consciousness and *general convulsion*. In the parieto-occipital region the lights may be flashing or mov-

ing, causing giddiness and even nystagmus, followed by unconsciousness and general convulsion. From lesions in the temporal gyri the general convulsion is often preceded by noises, hyperacusis, tinnitus or even music, which may be accompanied by vertigo or hallucinations of unpleasant odors. Tumors near the uncinate gyrus commonly cause an aura of bad smells or taste with automatic smacking movements of the lips before the convulsion. Thus much physiological knowledge has been corroborated on the human by surgeons using the electrode and by Nature using local lesions.

Lesions of the frontal lobe are particularly interesting. Since this is the largest association area of the brain without any receiving stations for special senses (as in the parietal, temporal and occipital lobes) one would expect little or no aura. This is the case: the patient usually begins his attack with a blank stare, losing consciousness at once, but not losing motor control, for he may then perform complex movements, walk about doing aimless things and mumbling. In more sudden attacks he may turn his head to the side away from the lesion, and then turn his whole body, even spinning around two or three times before falling in a general convulsion.

All this about cortical epilepsy, however, is rather special. It is particularly interesting because of its localizing value and because patients with cortical lesions are most open to surgical help. But the recent work of Gibbs and Gibbs<sup>9</sup> shows that (in cats) the deeper structures where the rhinencephalon lies over the diencephalon give convulsions in response to electrical stimuli more easily than even the motor area of the cortex. It is as if certain tracts and cells here would set off a convulsive mechanism with greater ease than others. The fact that deep temporal lobe tumors are especially likely to be associated with convulsions is of interest in this connection. But the search for a "convulsive center" is illusory. There can be no "center" for disorganization or disintegration. Probably, because of special connections, easily traveled paths, or ease of conduction in certain areas, an electrode placed in such loci will more easily cause the unbridled activity we call a convulsion, than an electrode placed elsewhere. We know that stimulation of less organized brains is more likely to cause convulsions than stimulation of thoroughly organized ones; *e. g.*, the convul-



sions of childhood,<sup>10</sup> and there are experiments showing that after injury the threshold for convulsions is lowered.<sup>11</sup> Myelination is quite incomplete in the human before the fourth year and convulsions can be easily precipitated in these years by almost any foreign element of excessive stimulation. This is perhaps because of less than normal spread; *i. e.*, *short-circuiting*. In chronic encephalitis, or postencephalitic states, there may be gliosis of the brain and the formation of connective tissue scars; cerebral hemorrhage and trauma may act in much the same way, and also the chronic degenerative diseases. It may be that reduction of the number of available association pathways for nerve impulses to travel is the important factor in all these extensive lesions. This, theoretically, could cause a "short-circuiting" of afferent stimuli making them discharge over efferent tracts without the normal delay caused by spreading through the wide association areas of the cortex.<sup>12</sup> Such short-circuited discharge might well be explosive and disorderly and cause seizures of various sorts. Other chronic processes, such as arteriosclerosis, senile degeneration, chronic arachnoiditis and porencephalic cysts, may also cause seizures by tissue destruction and this "short-circuiting" mechanism. Tumors and cysts obviously cause increased intracranial pressure and damage to the tissue, but the fact that tumors of the hindbrain rarely if ever cause convulsions<sup>13</sup> and that convulsions are most common when the motor cortex is involved, indicate that there is direct irritation of motor nerve cells. It might be that these tumors interfere with circulation and cause local stasis with edema, anoxemia and softening, but such changes would cause death of nerve cells and the convulsive symptoms would soon cease; clinical experience shows that convulsions caused by tumors impinging on the motor area may occur over periods of several years.

It is probable that vasomotor abnormality in the brain as a primary cause of seizure has been overemphasized by some authors<sup>14</sup>; but that changes in cerebral blood flow may precipitate convulsions, is indisputable. There are six conditions on the list that obviously work through anoxemia of the brain. All of these six cause widespread anoxemia and convulsions. The first is Stokes-Adams syndrome in which, as reported by Mackenzie, if the heart block lasted for ten sec-

nds only, unconsciousness alone occurred; but if it lasted for seventeen seconds, there was also convulsion. The onset of paroxysmal tachycardia may also be attended by seizures. Pressure on the carotid sinus with the sharp fall in blood pressure may precipitate a convulsion, but sometimes the convulsion occurs without the fall in general blood pressure.<sup>15</sup> The other two mechanisms that can be relied on regularly to produce convulsions are carbon monoxide poisoning and mechanical asphyxia, as in strangulation. In experimental animals it is always possible to produce convulsions by ligating the arteries that supply the brain, and also by limiting the oxygen that is inhaled. In patients having very frequent petit mal, Lennox<sup>16a</sup> has shown that seizures can be induced by a degree of oxygen lack that will not affect normal persons, and also by an impending induced syncope. It is obvious, however, that these conditions that cause general cerebral anoxemia are not the ordinary causes of seizures as seen in epileptic patients. Gibbs and Lennox<sup>16</sup> have shown that no *general* change in cerebral blood flow occurs before a fit. On the other hand, *local* areas of cerebral anemia may set off the neurological mechanism that causes fits<sup>17</sup> and there is good histological evidence that many convulsions, including puerperal eclampsia, are due to vascular spasm in the brain.<sup>18</sup> Some cases of Raynaud's disease and of angioneurotic edema are accompanied by seizures.

The effect of emotion and environmental stress upon epilepsy has long been recognized. Increased emotional stimuli<sup>19</sup> especially if repressed, usually increase the number of attacks. Special situations may act as conditioned stimuli and set off fits that thus are practically conditioned reflexes.<sup>20</sup> Examples of this are common in practice and patients showing possible psychological factors should be studied intensively. For example, a young woman of twenty-one was referred to me in 1932. At the age of nine she had cranial trauma and two months later onset of convulsions. She has seen many doctors and had many treatments. A régime of high enemas at twelve did no good; a nine months' trial of dehydration at eighteen made her worse; "lutein" has helped her irregular menses, but has not affected her fits; luminal helped, but has been used excessively. Because the attacks began in the left leg and

because slight but distinct neurological abnormalities were noted on the left side, Dr. Wilder Penfield operated upon her at the age of nineteen and found adhesions over the right frontal lobe, excessive vascularity of the cortex and unstable arteries. These were actually observed in vascular spasm with concomitant anemia of the lower part of the motor cortex and convulsion especially in the left face.<sup>21</sup> Removal of the "trigger point" in the cortex, where a weak faradic current precipitated a convulsion (right superior frontal convolution) caused temporary hemiparesis, but eventual diminution in number and severity of the attacks. Eighteen months later she went through a severe emotional experience, thereafter there were more "minor seizures"; many of these were probably anxiety states as no clouding of consciousness was observed. The emotional element was great. Since the age of ten she had been supervised meticulously, her varied and prolonged treatments had given her the "invalid habit," she was full of self-pity, said she was "utterly lonely" and could not mix with other girls or boys of her own age. She had had no regular schooling and could get no job.

To evaluate all the factors mentioned in this complex picture is difficult, but important, if one is to help this girl who is not only epileptic but hypochondriacal, psychoneurotic and drugged with luminal, coffee and cigarettes. Charting the factors helps a great deal to make the problem concrete (Fig. 180). This is a "life-chart" drawn to indicate the dynamic factors in the patient's history. Each arrow represents one of the factors in the etiology of the present problem; *i. e.*, the fit. The lines suggest by their weight the severity of the abnormality and by their length the duration. Obviously all the factors contributing to the "nervous load" are not equally important from an etiological standpoint, but by looking at the whole chart one gets an idea of the interaction of the different elements. Certainly the main abnormality, represented by the heaviest arrow, is the *cerebral cortical scar* present since the age of nine; this is the principal cause of the fits; it has been treated surgically in the most scientific manner; nothing more can be done.

The arteries of the brain were observed in spasm; there are other indications of *vasomotor instability*, but the poor

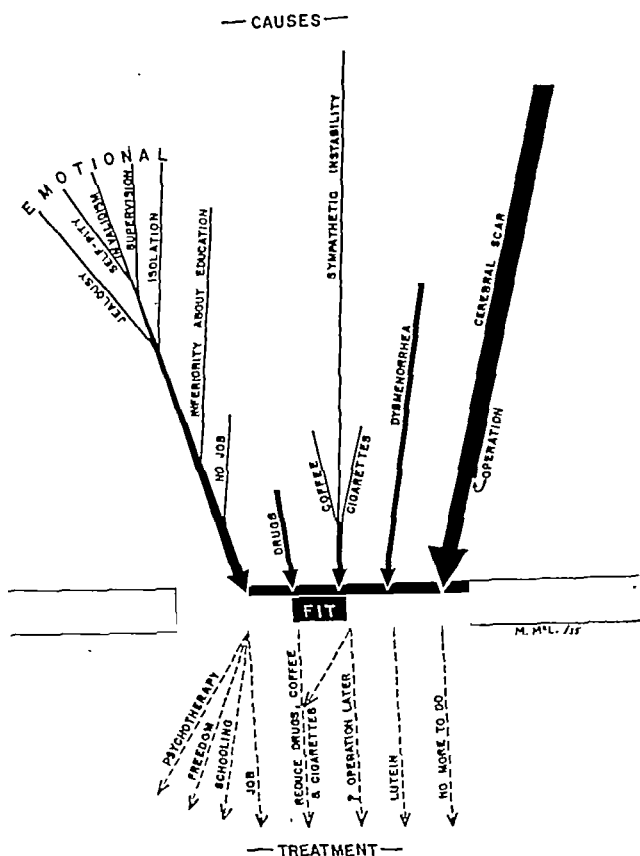


Fig. 180.—The diagram is drawn to bring together in the physician's and patient's minds the etiological factors in a dynamic way. Above are the various causes, indicated by arrows, converging on the patient at the time of examination. These arrows, great and small, make a burden too great for the patient's nervous system and a fit results. Obviously the main cause of convulsions in this case is the cerebral scar, a heavy burden for many years, hence represented as a long and heavy arrow. The operation improved the cerebral lesion and fits became fewer thereafter, hence the notch in the big arrow. The other arrows represent other pathological factors in the patient's life. These are individually of slight importance as compared to the cerebral lesion, but added together they constitute an important problem and probably act as the precipitating cause of many attacks. Below is shown what was done for treatment of each pathological cause. For the cerebral scar nothing more can be done. For the dysmenorrhea lutein was given. To counteract her vasomotor instability she was made to cut down on coffee, cigarettes and drugs (a sympathectomy might possibly be considered later). To improve her emotional instability, she is taken away from anxious supervision, given a job, schooling, and some psychotherapy. These are adjuncts to the surgical therapy, but they make this difference to the girl: she stops being an invalid, lives a practically normal life, is happy and has fewer fits.

general hygiene of the patient may be responsible for this, especially the excessive coffee and cigarettes. An operation to denervate the cerebral arteries by sympathectomy was considered, but it was deemed unwise to operate again upon her. General hygiene, physical training, reducing coffee and cigarettes, all have helped the vasomotor instability.

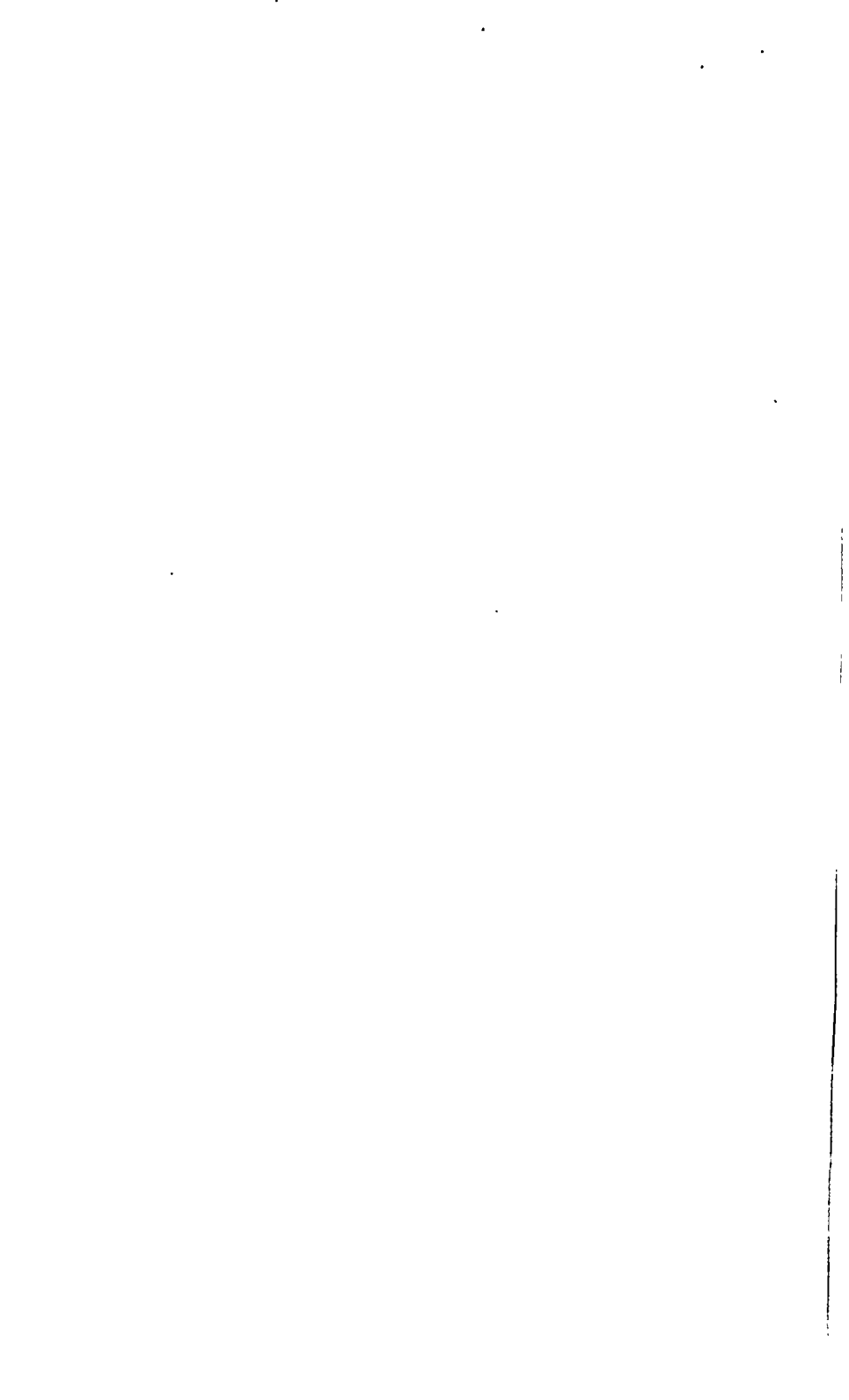
*Luminal* has been used for several years; for the last two years 3 grains per day had been given. She has been rather depressed and dozey from this and her eyes have often looked sleepy. This medicine was discontinued for a period of observation, during which general hygiene, both mental and physical, was emphasized. There was no increase in the number of seizures. *Lutein* has been found to help her painful and irregular menses; this has been continued.

The *emotional factors* are numerous. Taken singly they do not seem important; added together, however, they make a burden of anxiety, unhappiness and self-pity that is devastating; the patient was having no satisfaction out of life. It is here that one feels most hopeful about therapy. The patient needed schooling and training to give her self-confidence; she was taken from home and put under less fearful and more objective supervision. This resulted in a new feeling of freedom. A job was arranged for her part time. Psychotherapy was tried and gave her insight into what was being done for her, but otherwise it had little effect and was soon discontinued. It was the environmental treatment that helped most. During the past two years she has had only two attacks.

When such a "new deal" can be arranged for a patient, there is reason for optimism regarding the prognosis even in cases of "traumatic epilepsy." The fact that one has a scar in one's brain does not make convulsions a certain result. It is a case of summation of nervous load. When many of the factors indicated by the arrows impinge on the patient's nervous system at once, a seizure results. It is a case of the "camel's back" and many "straws." One cannot take away the scar which is the original and biggest part of the nervous load, but if the other straws are removed, the patient may well go on for years without a seizure. Symptomatically she may be "cured." And that is all the patient cares about.

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## CLINIC OF DR. G. P. GRABFIELD

PETER BENT BRIGHAM HOSPITAL

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### THE TREATMENT OF INSOMNIA

THE treatment of insomnia is a subject which can be considered from many angles. It seems wise to limit the discussion to certain phases of the subject, in order to avoid excursions into the realm of psychiatry. Texts of internal medicine do not recognize such a condition. It must be admitted that no clear, short definition can be stated. Yet all know what is meant by the term, though from an etymological point of view it simply means lack of sleep from any cause. It may be due to pain, discomfort, dyspnea, frequency, diarrhea, itching or any symptom that forces itself upon the sensorium. However, the usual idea of insomnia as a medical problem is that of sleeplessness unconnected with somatic symptoms. If sleeplessness is due to some definite cause, such as one of those enumerated above, treatment is necessarily directed to the relief of the underlying symptom. True insomnia, therefore, we may define as sleeplessness due to no underlying stimulation preventing sleep or awakening the sufferer. The condition may assume different forms.

First and most common is difficulty in going to sleep, second, awakening early and inability to sleep again, third, periods of wakefulness in the middle of the night and finally, a reversal of the sleep mechanism with wakefulness at night and sleep by day. The cause of the first three types usually is habit or some emotional disturbance either acute or as a manifestation of a psychoneurosis. The last, most distressing form is almost exclusively found in cerebral arteriosclerosis and usually is accompanied by other manifestations of senility.

Since it is axiomatic that the treatment of any symptom should be directed to its cause, and since the usual cause of



insomnia is either habit or a psychoneurosis, it is obvious that treatment must be directed against these underlying conditions. Many tricks have been advised to aid the sleepless sufferer; counting sheep, voluntary relaxation, lying in one position and various other methods of autohypnosis. While such methods may be successful in breaking bad sleeping habits or even in overcoming a superficial psychoneurosis, it is poor therapy to treat psychoneuroses by suggestion alone, and in every persistent case adequate psychotherapy applied by an expert is necessary. Often reassurance as to the harmlessness of sleeplessness is sufficient to break the vicious circle of wakefulness intensified by the worry of not sleeping and the consequent effect on the following day's efficiency. Certainly lying quietly in bed is often adequate preparation for the daytime tasks even though the hours spent in actual sleep be few. It is outside the scope of this clinic to discuss further the psychotherapy of insomnia. However, in connection with the foregoing, the indications for the use of hypnotic drugs may be concisely formulated. The following four indications for the use of soporific drugs seem clear:

1. Where sleeplessness can be foreseen as the result of an acute situation of short duration.
2. Where wakefulness is clearly due to an obvious cause, and the symptomatic relief will aid in the treatment.
3. Where the cause is unclear, but relief is urgently demanded, and no danger of masking night symptoms is present.
4. In the reversal of the sleep mechanism in cerebral arteriosclerosis.

The first group includes such situations as the near relatives of a deceased person before the funeral, the first night in the hospital and others that will readily come to the reader's mind. In the second group are such cases as discomfort from any of the causes previously enumerated. Even though the cause is unclear, and no definite disturbing symptoms are present, immediate relief of the third group of sufferers will aid subsequent therapy, even if the cause be psychic. Finally, relief in the fourth group demands the utmost care in the use of drugs to change the mechanism without intensifying it by the late action of the soporifics. This brings us to a further point to be remembered in the use of hypnotic drugs.

This consideration concerns the time and duration of action of the drug exhibited in relation to the intensity, duration and period of sleeplessness. It is well known that there are three types of insomnia, the commonest being difficulty in getting to sleep. "I stay up until I am sleepy, but getting ready for bed wakes me up, and I toss for hours," says the patient. The next tells of awakening in the middle of the night and lying awake for a period invariably longer to the patient than observation by the clock would indicate. And finally, there are the patients who awaken so early in the morning that they outdo the proverbial lark. Of course, any combination of these types may exist. The drug to be used in any given situation must be such as to combat the symptom of which the patient complains. It is all too easy and, unfortunately, too common, to give patients large doses of some momentarily fashionable or advertised hypnotic, when small doses of a judiciously selected drug would provide the relief desired. If we use the above criteria we may classify the hypnotics according to the rapidity and duration of their action. In general, these two properties are parallel. It is also an advantage to reduce the list to the smallest number that will serve. All hypnotic drugs have undesirable side actions in large doses or in susceptible individuals, and there must be included in any list a sufficient variety to allow for such idiosyncrasies.

Considering first those with rapid action over a comparatively short period of time suitable for patients unable to get to sleep, we find first of all paraldehyde and chloral both of which have stood the test of time. The obvious disadvantage of paraldehyde lies in its odor on the breath the following day, but this is often more than compensated by its efficacy and above all by the practical absence of toxicity. It must be remembered, however, that the combined use of morphine and paraldehyde is highly toxic. Chloral is undoubtedly the most useful of all the hypnotics and the cheapest. Given well diluted in water it produces sleep within an hour, and in proper doses (0.3–0.6 Gm., 5–10 grains) is entirely harmless even in heart disease. There is no doubt that in toxic doses it kills by its effect on the heart, but the fear of this side action has been engendered by the large dosage that has always been

recommended up to the last few years. None the less, it is not the hypnotic of choice in heart disease, though it may be used, if for some reason the barbitals and paraldehyde are contraindicated in a given patient. For quick action of short duration two of the barbiturate series recommend themselves. Pentobarbital (1-2 grains, 60-120 mg.) has proved very useful, and it may be that "evipal," a newer one of the series with a very rapid evanescent anesthetic action, when given intravenously, will prove useful as a short duration hypnotic with prompt action, when given by mouth.

Barbital itself is still the most satisfactory drug, where more prolonged and less prompt action is desired. In all these drugs both intensity and duration of action are increased with increasing doses. If, therefore, more than 0.6 Gm. (10 grains) of barbital is found necessary to produce the effect desired, another drug should be used. Comparable to barbital but of another chemical constitution is "sabromin," considerably more expensive than barbital but with prolonged effects. Sulphonethylmethane has fallen into disuse on account of the long period before it acts and because of its prolonged stay in the body. However, these very qualities can be utilized in selected cases. It is usually effective five to seven hours after administration and is particularly useful in the second group of patients. Its action, however, is prolonged, and it may leave a certain amount of drowsiness the next day. Furthermore, repetition over a comparatively short period, even in ordinary doses, may lead to liver damage. In occasional selected cases for short periods it may be extremely useful, especially in supplementing the action of some of the shorter acting drugs. Thus the combination of barbital with sulphonethylmethane given an hour or two before bedtime may prove more satisfactory than double the dose of barbital for producing a deep sleep throughout the night. This evidence of synergism suggests that other combinations might prove equally useful. The unfortunate one between paraldehyde and morphine has been mentioned and another between chloral and alcohol is well known, even to the underworld, in the form of "knock-out drops." Synergism between the hypnotics and antipyretics (analgetics) has been fairly well studied in some instances. This should be utilized when pain

or discomfort is associated with insomnia. While the anti-pyretic drugs of the types, acetyl salicylic acid, amidopyrine and acetphenetidine have almost no hypnotic actions, the soporifics discussed have equally little effect on pain. Yet combinations of these two groups of drugs enhances the effects of each. In this connection it is well to remember that both morphine and codeine are inefficient hypnotics as compared with the drugs discussed. Finally, on certain occasions sleep is disturbed, largely by motor restlessness, "the fidgets," not directly associated with cerebral activity. Under such circumstances phenobarbital ("luminal") and the bromides are most useful, but their effects are prolonged on a comparatively low level of intensity. Both are poor hypnotics in the strict sense of the term and produce their quieting effect by their depression of the motor side of the central nervous system; neither should be used as simple soporifics.

Care in the selection of the soporific agent in relation to the exact symptomatology will yield excellent results. Only a small number of the vast array of sleep producing drugs on the market need be in the armamentarium of the physician. Careful clinical observation of all the possibilities of a few drugs is a suitable problem for study in private practice. Laboratory research is active in this field, but it is to be hoped that careful clinical observation checking careful pharmacologic experiment will prevent the present increase by geometric progression in the numbers of hypnotic drugs varying but little from the standard and offering no real advance in therapeutic efficiency.



## CLINIC OF DR. RICHARD M. SMITH

### CHILDREN'S HOSPITAL

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#### ABDOMINAL PAIN IN CHILDREN

ABDOMINAL pain is one of the most frequent conditions in children for which the physician is consulted. The pain may be acute and seen in a first severe attack or chronic and encountered after many recurring episodes of moderate and varying intensity. The first severe acute attack of pain is often an emergency in the sense that it requires an immediate decision in relation to the necessity for surgical intervention. Too great emphasis cannot be placed upon the requirement for superior surgical technic when an operation is indicated, but it is to be remembered also that a high degree of professional skill is needed to elicit and interpret correctly the history and physical findings. Despite the urgency of the situation a careful study of the patient should be made and all possible explanations for the pain should be considered. There must be the exercise of sound judgment for improper treatment, based upon an incorrect diagnosis, may result in the death of the child. When there have been repeated attacks of pain in the abdomen the emergency may be less acute but the difficulty in diagnosis even greater.

In dealing with children as contrasted with adults there are certain things which need especial consideration. The history of any illness is of great importance but it is difficult to obtain a reliable history of an illness in a child. In infants and young children the story must be obtained from a parent or nurse. One should ask simple questions which can be answered briefly—directed toward securing exact information if possible. It is easy for a lay person to give an interpretation of facts instead of the facts themselves. Sometimes a clear description of what has happened is given by the mother or nurse. Frequently, however, the account is confused by a

limited power of observation or by extreme apprehension and an exaggerated emphasis on trivial matters. One needs to consider the temperament of the person who is giving the history. Familiarity with the family is of great assistance. When the history is obtained wholly or in part from the child one must remember the limitations of the informant. Children rarely express themselves with precision. Usually they complain less than adults and often will talk very little when they are sick. Crying may be the only presenting symptom. Serious disease within the peritoneal cavity may exist without complaint of abdominal pain either because as in infants speech has not yet been acquired or as in young children the ability to localize pain has not yet been developed. Pain apparently in the abdomen may be local discomfort caused by disease elsewhere in the body. Despite the handicaps under which one works it still remains true that the history is of prime importance.

Another consideration to be constantly borne in mind in working with children is the frequency with which the pathologic condition is dependent upon some congenital anomaly. Such anomalies are not uncommon in connection with the group of diseases which are under discussion.

Pain in the abdomen may be caused by disease or disturbed function

1. of some part of the gastro-intestinal tract.
2. of some other abdominal viscus or structure.
3. in some other part of the body and the pain referred to the abdomen.

I. Abdominal pain caused by disease or disturbed function of some part of the gastro-intestinal tract.

Congenital hypertrophic stenosis of the pylorus.

Intussusception.

Intestinal obstruction.

Appendicitis.

Ulcer of stomach or duodenum.

Colitis.

Spastic colon.

Indigestion—"colic" in infants.

**Congenital Hypertrophic Stenosis of the Pylorus.**—

This is a condition the first symptoms of which appear dur-

ing the early weeks of life, rarely beginning immediately after birth. Crying is the obvious expression of pain. The pathologic finding consists of a stricture, partial or complete, at the pylorus, due to an hypertrophy of the circular muscle fibers and their replacement by firm fibrous tissue. The presenting symptom is vomiting of increasing severity and projectile in character. Constipation is an early feature, becoming more marked as the obstruction increases. The bulk of the fecal content decreases until the stools are composed entirely of intestinal secretions with no true fecal residue. There is stationary or loss of weight. Physical examination reveals peristaltic waves in the upper abdomen traveling from left to right (gastric) and a tumor palpable at the pylorus. These findings are most easily elicited just after a feeding followed by vomiting. Often the tumor is felt easily, but at times repeated examinations are necessary. The treatment is surgical and should be instituted as soon as the diagnosis has been established. If the infant shows marked dehydration intravenous and subcutaneous fluids should be given before operation. The prognosis is favorable if the operation is performed by a surgeon with experience in this particular procedure and has not been too long delayed.

**Intussusception.**—The history is of particular importance in this condition. An infant, previously well, often breast fed, has sudden severe cramp-like pain in the abdomen evidenced by a sharp cry and by drawing up of the legs upon the abdomen. Usually vomiting occurs promptly and shortly the baby passes a stool containing blood and mucus. Sometimes there is no blood in the stool or even there may be no bowel movement. There may be recurrences of the pain at frequent intervals with or without vomiting. If seen soon after the first attack the physical examination may be entirely negative, but there may be a marked degree of shock. Eventually a sausage-shaped tumor is palpable in the abdomen. Rectal examination may reveal the head of the invaginating portion of the intestine often just within the anal sphincter. The examining finger will usually show bloody mucus. Roentgen-ray examination without barium may show the point of obstruction and is useful in confirming the diagnosis. The treatment is surgical. The prognosis depends upon the time



at which operation is performed. If done early it is good; if late, the risk is greatly increased, rising directly with the time between the onset of symptoms and the operative interference. It is not desirable to try reduction of the intussusception with enemata.

**Intestinal Obstruction.**—We shall consider here only those instances in which obstruction is due to mechanical causes. Adhesions dependent upon a previous inflammatory process in the abdomen or secondary to a surgical operation may produce a similar picture. There may be complete or partial atresia of almost any part of the gastro-intestinal tract or other developmental defects such as incomplete relation of the cecum. Except when complete obstruction occurs the symptoms may be absent for many months or even years, or may be intermittent in character. Vomiting is the outstanding symptom. Pain is present in greater or less degree. The stools become scanty, depending upon the degree of the obstruction. There is usually abdominal distention with visible peristalsis. Dehydration may be extreme if the vomiting is severe. Roentgen-ray examination without barium often furnishes conclusive evidence and localizes the point of obstruction.

**Appendicitis.**—Appendicitis is a fairly common disease in childhood but is unusual in infants. Recurring attacks are frequent. Often the diagnosis is missed and the symptoms explained on the basis of indigestion. The striking feature of the condition as it occurs in children is the fact that a severe pathologic condition may be present with very slight symptoms and few physical signs. In over one half of the children admitted to the Children's Hospital for appendectomy the appendix had perforated when first seen (Hudson).

The etiology of appendicitis in childhood is not different from that in adults and need not be discussed in detail. It should be borne in mind, however, that true appendicular colic is not unusual in children associated with and dependent upon an inflammatory condition in the colon.

A typical history is as follows. A child who has been previously well is nauseated and vomits perhaps once or possibly two or three times. Associated with the nausea and usually before the vomiting there may be some abdominal pain,

but frequently it is not severe or is absent and often is of short duration. Sometimes pain occurs without vomiting. Movements of the bowels may be normal. The symptoms may entirely disappear at the end of a few hours and the child appear perfectly well, but if seen at the end of this period the physical signs of appendicitis may be present. Not infrequently the attack is so mild that no physician is called and recovery takes place. It is only when a child is seen in subsequent and somewhat more severe attacks that a presumptive diagnosis in relation to the previous attacks can be made. Occasionally the pain may be very severe and vomiting may be persistent, but this history is the exception rather than the rule. On physical examination the children do not appear to be very sick. There is a slight elevation of temperature, frequently not above  $100^{\circ}$  F. by rectum, or may even be normal and a moderate polymorphonuclear leukocytosis. It is possible to have a gangrenous appendix and a normal white count. Examination of the abdomen shows slight tenderness and a little spasm usually located in the right lower quadrant of the abdomen, sometimes in the right rectus muscle. True spasm, no matter how slight, should always be considered of pathologic significance. Pressure over other parts of the abdomen, especially over the left lower quadrant, may cause pain in the right lower quadrant. Rectal examination is important and frequently elicits a tender mass high up on the right just below the brim of the pelvis.

There are a number of anatomical considerations which modify materially the physical signs of appendicitis in childhood and these should be constantly borne in mind. The cecum, and therefore the appendix, is freely movable because of the long mesocecum. As a result, the appendix may be located in other portions of the abdominal cavity than the right lower quadrant. It may be on the left side instead of on the right. The appendix itself is also longer than it is in the adult and this adds further to its variety of location. When the appendix extends into the pelvis, as is frequently the case, there may be no physical signs in the abdomen. The diagnosis can be made only by rectal examination. In pelvic appendicitis not only are there no physical signs in the abdomen but there is practically no abdominal pain, but there is

discomfort on voiding or on emptying the bowel. The local inflammatory process may produce diarrhea or because of the pain there may be constipation or retention of urine. The appendix, because of its additional mobility, may be situated in the right flank and outside the cecum with the cecum over it and in front. The diagnosis, under these conditions, may be confused with an acute infection of the kidney, or if the inflammatory process extends downward, tenderness may be present just above the iliac crest. The appendix may be behind the cecum and the ileum and extend inward. This is a particularly dangerous situation because of the likelihood of general peritonitis developing.

A diagnosis of appendicitis should never be made simply on the basis of a local examination of the abdomen. It is important to obtain a careful and accurate history and to make a complete physical examination.

**Ulcer of Stomach or Duodenum.**—Ulcerations in the upper portion of the gastro-intestinal tract are not common in children but they do occur, and should be kept in mind in making a differential diagnosis in abdominal conditions. The vomiting of blood or blood-tinged mucus is of particular significance.

**Colitis.**—Ulcerations in the colon are very common in children. They may be dependent upon infection with one of a variety of organisms of the dysentery group. Tuberculous colitis occurs in rare instances. The onset of colitis may be very sudden with high temperature, convulsions, and marked prostration. Diarrhea may be absent for several days. Vomiting may be a prominent symptom. Pain may be slight or severe. Physical examination of the abdomen may be negative. One should remember the possibility of colitis in any acutely ill child when the diagnosis of some other condition is not clearly established. A culture from the stools is necessary for confirmation of the diagnosis.

**Spastic Colon.**—A spastic colon is usually associated with a history of long-standing constipation. There may be recurring attacks of abdominal pain, often with vomiting and elevation of temperature. Physical examination reveals abdominal distention of variable degree and it is usually possible to palpate the enlarged colon filled with hard fecal masses.

A barium enema, especially if observation is made on the fluoroscopic screen during the injection, shows an enlarged colon. There is sometimes resistance to complete filling, particularly at the flexures, where fecal residue has accumulated. Emptying of the colon after the enema may be incomplete and the haustral markings obliterated or reduced in depth.

**Indigestion.**—Under normal circumstances the processes of digestion go forward without our conscious knowledge and without producing any uncomfortable sensations. Due to a variety of causes, however, stimuli may be sent forth from the digestive tract, which cause mild discomfort or severe pain. When one has abdominal pain from this cause we say it is due to indigestion or colic. This diagnosis is difficult to make on the basis of positive evidence and is to be accepted only after all other possible causes of the symptoms have been eliminated.

A recent medical graduate in discussing his new experiences in practice outside of the hospital said that he had not yet seen a single case of unrotated cecum but that he had encountered numerous infants with "colic," and nobody had ever told him anything about it or what to do for it.

Colic is a term used to describe a condition seen in infants, characterized by pain in the abdomen associated with the digestion of food. Infants with colic are very fussy and restless and sleep poorly. Often they cry vigorously, especially at night. They are the babies who furnish the basis for many jibes at the solicitous father who walks the floor and the opportunity for the patent medicine vendors to dispose of "soothing syrups." Colic is seen most often in infants under three months of age. It often recurs at the same hour of the day or night.

It is not always easy to find out why some babies have colic. It is dependent upon a variety of conditions. Improper food is blamed most frequently by parents, but is the important factor less often than matters of hygiene and technic of feeding. In breast-fed babies the food may be unsuitable because the mother is tired or worried or of a temperament which makes lactation difficult. The attack upon colic, under these circumstances, should be directed toward establishing a better regimen for the mother but success is not easily attained.

In the bottle-fed baby some modification in the formula may be desirable, but if the food has been properly selected in relation to essential elements and their proportions and is adequate in amount, colic from this cause is rare. Most bottle-fed babies with colic are the victims of poor management. The feedings are given irregularly, the routine of bathing and care is haphazard, and attention is given to the point of fatigue. Food is not digested well because the processes of digestion are never allowed to proceed under normal undisturbed conditions. Sometimes the technic of giving the bottle is such that air is swallowed in large quantities, or the baby has to suck so hard as to become fatigued, or some of the other many possible errors are committed. The approach to the problem of treatment should be first to go over carefully the content of the food to satisfy oneself that it is correct, then to discuss in detail the routine of the baby's life. A long process of education may be necessary to bring about the proper daily care. Sometimes before relief of the condition is accomplished it will be necessary to introduce into the home a new person to whom the entire care of the baby is entrusted and who will carry out directions accurately. A demonstration by a short period of hospitalization is often effective. As a rule, a "colicky" baby is cured at once when placed on hospital routine, even when the food remains the same as that which was given at home. Relief of distress at the time of an attack of colic is usually possible by the giving of an enema and administering a small amount of warm sodium bicarbonate solution (1 drachm to 8 ounces of water) by mouth. Heat and mild massage to the abdomen is also helpful. It hardly needs to be emphasized that colic should be diagnosed only by exclusion of other pathologic conditions. One sees an infant crying hard with legs flexed on the abdomen, without fever—the question which presents itself for an answer is why? One must be satisfied that no other condition is present before assuming that the baby has colic.

II. Abdominal pain caused by disease or disturbed function in some abdominal viscus or structure other than the gastro-intestinal tract.

Diseases of the urinary tract.

Liver and gallbladder disease.

Pancreatitis.

Tumors.

Tuberculosis.

Infection—nontuberculous.

Purpura.

Allergy.

**Diseases of the Urinary Tract.**—Nephritis rarely causes abdominal pain. Acute infection of the kidney, on the other hand, is one of the common conditions giving rise to this complaint. Physical examination may reveal tenderness and spasm at the costovertebral angle and often the kidney is palpable. The diagnosis of urinary tract infection is confirmed by the finding of pus in the urine. One must remember that not uncommonly the underlying pathologic lesion is a congenital anomaly which interferes with the free passage of urine at some point between the kidney and the external urinary orifice. There may or may not be an associated hydronephrosis. Careful studies with cystogram, intravenous, or retrograde pyelography are necessary to determine the exact character of the lesion and indicate the appropriate treatment, either medical or surgical.

Renal stones are quite common in children and not rare even in infants. Pain may not be a prominent symptom. Occasionally stones in the bladder occur in children.

Renal tumors may often attain a large size beyond the stage where operative removal is possible without giving rise to pain.

Perinephric abscess is rare in children.

**Liver and Gallbladder Disease.**—Acute catarrhal jaundice may cause pain in the right upper quadrant of the abdomen. Gallbladder disease, with or without stones, is not common in children. Other diseases of the liver causing pain are rare. Chronic passive congestion dependent upon cardiac decompensation is often very painful.

**Pancreatitis.**—Pancreatitis is very rare in children. Occasionally the pancreas is affected in epidemic parotitis (mumps).

**Tumors.**—A variety of tumors within the abdominal cavity may be found in children. Some of these give pain only when they have reached a large size, causing tension upon the capsule of an organ or have metastasized to glands, particularly

the retroperitoneal glands, and cause pain by the same mechanism. An ovarian cyst, often with a pedicle which becomes twisted, may cause severe abdominal pain and present, on examination, the findings of an acute surgical abdomen.

**Tuberculosis.**—Tuberculous peritonitis and adenitis are both encountered much too frequently in infants and children. Peritonitis is more common under three years of age. Obstruction is often a prominent feature. The onset may be insidious and the condition be far advanced before there are sufficient symptoms to lead the parents to consult a physician. Adenitis may also be unsuspected for a considerable time and if the glands in the right lower quadrant are involved, as is often the case, the differential diagnosis from appendicitis may be difficult and sometimes is made only at the time of operation. Except when an operation cannot safely be postponed, the tuberculin test is of great assistance in diagnosis and if the condition is of long standing the roentgen ray may disclose beginning deposition of calcium.

**Nontuberculous Infections of the Abdomen.**—Peritonitis and adenitis due to organisms other than the tubercle bacillus are common in children. Thrombophlebitis of the portal vein or some of its tributaries is not rare. Most frequently these infections are associated with infection in some other part of the body, primarily of the respiratory tract, or they may be the first presenting sign of a general septicemia or as the only evident focus of infection. It is important to appreciate the significance of this association because of the influence upon treatment. Attention should be directed primarily toward the general infection. Peritonitis of this origin is better treated by conservative methods than by immediate operative interference. In adenitis the glands themselves require little consideration.

**Purpura.**—Not infrequently the abdominal lesions of purpura give rise to acute abdominal pain. A careful history with the finding of other evidences of purpura must be relied upon to establish the diagnosis.

**Allergy.**—Abdominal symptoms in allergic conditions are not rare. These symptoms may be the only manifestation of the disease at the time of an acute attack or even of a chronic state, but again the history, both familial and individual, to-

gether with other allergic symptoms, should serve to differentiate this form of allergy.

III. Diseases in which there is pain referred to the abdomen.

Respiratory tract infections.

Rheumatic fever.

Diabetes.

Roseola infantum.

Lead poisoning.

Spinal disease.

Intracranial disease.

**Respiratory Tract Infections.**—Mention has already been made of the abdominal complications of respiratory infection. There are also instances in which there is no specific lesion within the abdominal cavity but in which abdominal pain occurs. Pneumonia is a classical illustration. Physical examination may be confusing for there may be few or no signs in the chest but tenderness and spasm of the abdomen. Spasm of the abdominal muscles, which is caused by disease above the diaphragm, relaxes with firm steady pressure but increases if due to disease within the abdominal cavity. A roentgen ray of the chest may reveal early pulmonary congestion not detected by percussion and auscultation.

The toxins liberated from infectious processes in the respiratory tract may act upon the muscles of the intestines, producing enterospasm, or upon the gastric and intestinal secretions, causing "indigestion."

**Rheumatic Fever.**—Carditis associated with rheumatic fever may cause abdominal pain. The other signs of rheumatic fever should prevent a misinterpretation of this symptom.

**Diabetes.**—Diabetic acidosis may be accompanied by severe abdominal pain. The explanation for this symptom is not clear.

**Roseola Infantum.**—One of the important symptoms of roseola may be abdominal pain. The age of the patient, the high temperature, and the normal physical examination are of assistance in the diagnosis.

**Lead Poisoning.**—Occasionally in children lead poisoning



may cause cramplike abdominal pain associated with constipation. This is not as commonly the case as in adults.

**Spinal Diseases.**—No patient with abdominal pain should fail to have a careful examination of the spine. The roentgen ray may reveal osteomyelitis or tuberculosis.

**Intracranial Disease.**—Rarely children with intracranial disease or edema associated with renal disease complain of periodic abdominal pain.

With these conditions in mind, how should one approach the diagnosis in an infant or child who complains of abdominal pain or presents symptoms suggestive of disease within the peritoneal cavity? It is essential first to remember what has been said of the importance of the history. Not infrequently a correct diagnosis is dependent upon an accurate history. The age of the patient must be given consideration because of the relative frequency of congenital abnormalities in infants. A first acute attack often presents less of a problem than recurring attacks occurring over a long period of time.

The physical examination will be greatly facilitated if one can gain the confidence of the child. Time spent in accomplishing this is amply rewarded because of the difficulty of getting reliable signs in a child who is resisting examination. Much information is revealed by inspection and may be obtained while the history is being taken and one is becoming acquainted with the child. When one palpates the abdomen one should be sure to have warm clean hands. The movements should be slow and gentle. The child should be engaged in conversation if possible. Observation of the child's face will often indicate pain more definitely than replies to direct questions. One should inspect the abdomen for distention or visible peristalsis and examine for free fluid, palpable or enlarged viscera, for abnormal masses, tumors, or accumulated feces. The character of these masses is important. Tenderness or spasm, even if very slight, is of real significance. The relaxation of spasm under slow steady pressure indicates disease above the diaphragm rather than in the peritoneal cavity. Palpation of the abdomen is unsatisfactory when the bladder is full.

One should not be satisfied with the local examination, but make a complete physical examination. The lungs deserve

especial consideration. The roentgen ray may reveal early signs of pneumonia not detectable by auscultation and percussion. In examination of the heart one should look carefully for the sign of pericarditis. Search for signs of respiratory disease should include investigation of the nasal accessory sinuses and the ears. The skin may show petechiae or other indications of a general infection. Rectal examination should not be omitted but should be done after all other procedures have been completed.

Certain special examinations may be indicated and in children with a history of recurring attacks of abdominal pain should not be overlooked. The blood may show leukocytosis, abnormal cells, reduced platelets, or stippling of the erythrocytes. The urine may contain pus or blood or crystalline elements of significance. The intradermal tuberculin test is essential in the consideration of a diagnosis of tuberculosis. Intravenous and retrograde pyelography gives valuable information about kidney structure. Roentgen-ray examination of the abdomen may show renal calculi, calcified glands, intestinal obstruction or tumor, and after barium ingestion or enema abnormal condition of the stomach, intestine, or colon. The roentgen ray of the long bones may establish the presence of an excessive deposit of lead.

Not all of the possibilities to be considered in the diagnosis of the cause of abdominal pain in children have been considered but the more important diseases have been mentioned and some indication given of the technic to be followed in reaching a correct explanation of the signs and symptoms. The process is one of diagnosis by exclusion and should be subject to periodic review unless the symptoms cease under medical treatment based upon a provisional diagnosis or after corrective surgical interference.



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### THE CLINICAL SIGNIFICANCE AND TREATMENT OF VERTIGO, DIZZINESS, AND RELATED SYMPTOMS

THERE is a tendency among physicians and patients to use the term vertigo to include such symptoms as giddiness, dizziness and faintness. Hughlings Jackson<sup>1</sup> pointed out long ago, and Symonds<sup>2</sup> has more recently stressed the fact that patients do not accurately describe their sensations through the use of such loose terms. Our experience in this clinic with patients who complain of attacks which include such sensations has led us to separate these patients into two distinct groups as regards their subjective feeling.

One group of patients complains of attacks including sensations which may be classified as true vertigo. The patients are conscious of a subjective feeling that their environment is moving about them or that they are moving about their environment. These subjective movements follow an orderly pattern which in individual patients is similar in different attacks. The patient is able to describe accurately either the direction of, or the type of movement.

The other group, which is a much larger one, consists of patients whose subjective sensations are vague and much more difficult for them to describe accurately. These sensations are variously described as vertigo, giddiness, dizziness, weakness, unsteadiness, dimness of vision, and faintness. The multiplicity of symptoms of which these patients complain is probably due to their inability to find a term which will adequately describe their sensations. A sensation of movement of the body or of other objects sometimes occurs, but the movement is not orderly or in a direction which the patient

can describe. Such sensations are best described by the terms dizziness or faintness, and belong to that syndrome which, when severe, terminates in syncope. For practical purposes these subjective sensations may be looked upon as "pre-syncopal" in nature.

Thus in analyzing the subjective complaints of such a patient, it is important to determine whether he suffers from true vertigo or from symptoms of a syncopal nature. There are a few distinctive features which serve to differentiate these two symptom complexes in a majority of instances in addition to the patient's description of his subjective sensations. The most important differential point is that vertigo is rarely, if ever, accompanied or followed by syncope or a feeling of faintness. Attacks of vertigo occur as frequently when the patient is lying down as when he is upright, and the attack is not influenced by orthostatic changes. On the other hand, dizziness and syncope occur when the patient is in an upright standing or sitting position, except in a few isolated instances, and are relieved by lying down. Nystagmus is common with vertigo and rare with syncope. Nausea and vomiting occur with syncope but more often accompany vertigo.

#### VERTIGO

I should like to reemphasize that the sensation of vertigo is a subjective feeling in which the patient seems to move about his environment or the environment seems to move about the patient in a definite pattern. The attacks are usually identical in a given individual. Depending on its severity, the attack may be accompanied by nausea, vomiting, pallor and sweating, and the patient may stagger or fall to the ground without losing consciousness. The attacks appear to be self-limited as to duration and may last from a few minutes to several hours. In rare instances the vertigo is almost continuous.

It is probable that the mechanism of vertigo is reflex in nature and that the cerebellum plays a major rôle in the production of such a syndrome. Thus, it is apparent why sensory impulses from the semicircular canals and from the eye, both closely connected reflexly to each other and to the cerebellum, should cause vertigo so frequently. Less commonly, lesions of the cerebellum, of the eighth nerve, of cerebellar tracts in

the brain stem, and of other afferent pathways leading to the cerebellum may cause this symptom complex.

**Aural and Ocular Vertigo.**—The most common causes for vertigo are automobile or train sickness and sea sickness. The former is an ocular type of vertigo and is probably brought about by rapidly following moving objects with the eye. The vertigo that sometimes occurs in individuals who look from high places is also said to be ocular in type. Sea sickness is largely initiated in the semicircular canals but may be due, in part, to ocular reflexes as well. The nausea, vomiting and vertigo caused by whirling around or swinging is of a similar nature.

Aural vertigo commonly occurs from irritation or increased pressure in the semicircular canals resulting from hemorrhage, infection, and from positive or negative pressure in the canal due to middle ear disease. Irritation or infection in the external canal or middle ear may also cause vertigo.

**Ménière's Syndrome.**—Dandy<sup>3</sup> and others<sup>4</sup> have shown that this condition is fairly common and have suggested that the term Ménière's syndrome is more appropriate than the term, Ménière's disease. Ménière's disease is not well defined clinically and is variously used to denote hemorrhage into the labyrinth, labyrinthitis, or to include various other types of aural vertigo. As Dandy points out,<sup>3</sup> of the cases originally described by Ménière, the only one examined pathologically was found to have been suffering from what appeared to be acute purulent labyrinthitis.

The typical Ménière's attack is one of sudden vertigo which, when severe, is accompanied by nausea, vomiting, pallor and sweating. Unilateral deafness is also present, and is progressive. Tinnitus on the affected side may occur only during attacks or may be present constantly. Nystagmus is usually present during the attack. The patient may fall to the ground, but rarely, if ever, does he lose consciousness. The attacks may occur at any time, either in the horizontal or upright position and even during sleep. The duration of attack varies from a few minutes to several hours. In an individual patient the attacks may vary in severity, but the severe ones are quite similar as to duration and symptomatology. Sudden movements of the head, ocular stimulation

from watching the movement of crowds or riding in trains or automobiles, unusual noises and fatigue, or emotional reactions may be precipitating factors. For many attacks no exciting cause can be ascertained. The term, pseudo-Ménière's syndrome, is used by Dandy to describe attacks of a similar nature in which deafness is not present. Most otologists feel that Ménière's syndrome results from middle or inner ear disease, but Dandy feels that it is caused rather by functional abnormality of the eighth nerve or its vestibular branch.

**Vertigo Associated with Intracranial Lesions.**—Neville<sup>5</sup> and Symonds<sup>2</sup> have recently discussed the various intracranial lesions which may produce vertigo. Suffice it to say that true vertigo may result from lesions in the cerebellum, pons, cerebrum, and cerebellar tracts as well as from increased intracranial pressure. Such lesions may be in the forms of tumor, abscess, hemorrhage or thrombosis, particularly of the posterior cerebellar artery, multiple sclerosis, arteriosclerosis, and encephalitis. These lesions may be recognized by localizing manifestations other than vertigo. Cerebellopontine angle tumors, when associated with unilateral deafness and tinnitus, may closely simulate Ménière's syndrome, but the attacks are milder in nature and other cranial nerves are also involved.

**Vertigo Due to Neurosis.**—Mendel<sup>6</sup> and Leidler<sup>7</sup> describe true attacks of vertigo which occur in patients having all the characteristics of a neurosis and in whom no organic cause can be found. The vertigo tends to be present constantly and is not accompanied by deafness or tinnitus. Such patients do not respond to any form of treatment.

**Other Causes of Vertigo.**—Vertigo may be caused by "toxic" agents such as alcohol and may be a symptom of uremia. It is particularly prone to occur in enteric infections and gastric upsets in children.

**Treatment of Vertigo.**—Treatment largely resolves itself into specific therapy of the disease causing this symptom. In acute diseases of the middle ear and labyrinth, the vertigo may disappear when the infection subsides. In chronic disease of the middle ear local treatment may be of aid, but it is not entirely satisfactory. For persistent attacks of vertigo, general measures which tend to depress or alter reflex activity

should be carried out. Sedative drugs such as bromides and barbiturates, as in epilepsy, may lessen the severity and frequency of attacks. When psychic factors and fatigue play a rôle, proper corrective measures are of aid. Furstenberg, Lashmet, and Lathrop<sup>8</sup> advocate keeping such patients in a state of negative sodium balance and acidosis by means of administering 9 Gm. (540 grains) ammonium chloride daily with a low sodium diet. They have reported good results in 12 cases. Dandy<sup>3</sup> and Coleman<sup>4</sup> have obtained symptomatic cures in 42 patients suffering from Ménière's syndrome by surgical section of the eighth nerve. Such an operation appears to be safe in the hands of a competent surgeon, and should be advocated for patients suffering from repeated attacks of vertigo, tinnitus and unilateral deafness in whom intracranial lesions have been ruled out and other treatment has failed.

During the actual attack of vertigo, care should be taken to prevent the patient from injuring himself by falling. An ice-bag should be placed on the affected side and sedatives administered. The head should be placed in a position most comfortable to the patient. The attacks are self-limited and the patient soon learns when relief is to be expected.

#### DIZZINESS AND SYNCOPE

Observations and studies in this clinic<sup>9, 10, 11</sup> on a large number of patients complaining of attacks of syncope and related symptoms have demonstrated that the subjective sensations which precede fainting are similar, regardless of the cause, and can be clearly differentiated from vertigo. If true vertigo can be ruled out, dizziness, faintness, and similar terms represent symptoms which precede syncope; therefore, a discussion of such symptoms necessarily includes one of syncope also. The patient's description of such presyncopal sensations varies with the severity of the symptoms, with the nearness to the state of unconsciousness, and with the duration of symptoms before unconsciousness occurs; however, all sensations have certain definite characteristics. The patients variously describe their feeling as dizziness, weakness, faintness, unsteadiness, of "things going black before the eyes," a feeling as though they were going to faint or fall asleep, and "weak-



ness in the stomach." There is no subjective movement of the patient or his environment in a definite pattern as is encountered in true vertigo. The symptoms usually occur when the patient is sitting or standing, and are relieved by his lying down. Rarely do they occur when he is in a reclining position. Being an early manifestation of fainting, such dizziness is of course encountered among a great number of subjects in whom the syndrome does not progress to unconsciousness.

The mechanism and cause for various types of syncopal attacks have been extensively investigated by Weiss and his coworkers in this clinic<sup>9, 10</sup> and a summary of the entire subject by Dr. Weiss can be found in the current Oxford System of Medicine.<sup>11</sup> I shall discuss briefly only the most important causes for such symptoms.

**Vasovagal Syncope.**—The commonest cause for dizziness is that associated with vasovagal syncope,<sup>12</sup> which includes ordinary fainting attacks. Such attacks nearly always occur in the upright position, and are relieved by lying down. During typical attacks, the heart rate is often slow and the blood pressure low. The patient is pale, sweats profusely, and the skin and extremities are cold and clammy. In individual instances, any of these manifestations may be absent. The attack lasts from one half to two minutes and the patient usually feels well within a few minutes after recovery. The cause for such syncope is probably pooling of blood in the peripheral vascular bed, particularly in the splanchnic region. This causes a diminished return of the blood to the heart and results in cerebral anoxemia. Such pooling occurs more easily in the upright position, due to the added hydrostatic factor, as a result of decreased "tonus" in the peripheral vascular bed. As Weiss has pointed out, "this instability or loss of tonus may be a permanent constitutional characteristic; it may be the result of prolonged rest in the recumbent position; it may be caused by bacterial toxin or other chemical substances, or it may be a temporary nervous phenomenon of psychic or neurogenic origin."

Such syncope and related symptoms are frequently seen under circumstances where patients stand in one position for a varying period of time, as when soldiers stand at attention or when crowds stand in public gatherings. I am told that

a supply of smelling salts can be found in many beauty parlors for patrons who develop this type of dizziness when they sit with the curling electrodes in place and the head in a fixed upright position. The vasovagal type of dizziness is frequently encountered among patients convalescing from illness when they first assume the upright position. Psychic factors play a varying rôle in initiating or accentuating this syndrome and are the precipitating cause for dizziness or syncope encountered during venepuncture and hypodermic injections, at the sight of blood, in operating room "initiates," and following fright or other emotional reactions. Vasovagal syncope appears to be accentuated by a warm, humid atmosphere.

*Treatment* consists in correcting any factors which can be shown to contribute to or predispose to such a state. If emotional factors play a rôle, proper psychotherapy should be instituted. The patients should be reassured that such symptoms do not indicate heart disease, as this belief is held by lay people in general. As a rule, subjects who faint at the sight of blood, during injections, etc., can usually overcome this fault through their own efforts. Physical exercise and physical therapy and hydrotherapy are of aid in improving the tonus of the vasomotor system. Abdominal binders in some instances, and proper breathing and postural habits may be of aid. Patients who develop symptoms while standing in one position should form the habit of frequently shifting their weight from one leg to the other. Following prolonged bed rest, elderly patients should particularly be instructed to gradually resume the upright position and warned against standing up too soon. If organic disease is present it should be corrected whenever possible. Dietary deficiencies should likewise be corrected.

The actual attack of syncope or severe dizziness should be treated by first placing the patient in a comfortable horizontal position with the head downward. The clothing should be loosened, particularly about the neck, and cold towels or ice should be applied to the forehead and face. Olfactory stimulants, such as ammonia, seem to be of aid in aborting or shortening the attacks. Massage of the legs and abdomen may be necessary. If unconsciousness is prolonged and other

measures fail, 1 cc. (15 minims) of a 1: 10,000 solution of epinephrine may be given intravenously.

**Dizziness and Syncope of Carotid Sinus Origin.**—Abnormality of the carotid sinus mechanism has been found to be a not uncommon cause for dizziness and fainting, and detailed discussion of this syndrome by Weiss, Baker, Capps and myself can be found elsewhere.<sup>9, 10, 11, 13</sup> The carotid sinus is a plexus of nerves located in the arterial wall at the bifurcation of the carotid arteries. Briefly, the attacks are similar in nature to those encountered in other types of syncope. In the mild attacks, dizziness occurs without actual fainting. Pallor and sweating frequently accompany the attacks but may be absent. The relation of the attacks to the orthostatic position is similar to that of vasovagal syncope. The attacks usually last from one half to two minutes. The diagnosis depends upon reproducing the spontaneous attacks by pressure and massage of the carotid sinus, which is located in the neck just below the angle of the jaw. Pressure should never be exerted over both sides simultaneously. The spontaneous attacks may occur without any apparent cause or they may be initiated by turning the head, pressure from masses in the neck, extreme changes in position of the head either side-wise or upward, psychic and emotional upsets, menstruation and the menopause. Digitalis and dietary deficiency have been found to have a sensitizing effect on this mechanism. The syndrome occurs at any age but is more commonly encountered in the higher age groups, in which instances myocardial and vascular diseases play an important rôle. The symptoms may be due to cerebral anoxemia resulting from either a reflex heart block (vagal type) or a reflex depression of the blood pressure (depressor type); or from a direct central reflex in which no change in the heart rate or blood pressure occurs and the cerebral blood flow is normal (cerebral type).

*Treatment* consists first in correcting any predisposing factors. Accompanying organic disease such as central nervous system syphilis, cervical adenitis, digitalis intoxication, and dietary deficiency should receive specific treatment. When such symptoms occur with the menopause, glandular therapy might be of value. Patients in whom emotional factors predispose to the attacks should receive adequate psychotherapy.

By changing their trend of thought, by moving about, or through the use of other external stimuli such as smelling salts, pain, etc., the patients can frequently delay or abort both the spontaneous and induced attacks. The patient should be advised as regards turning the head and wearing clothes which press against the region of the carotid sinus, if such factors play a rôle in causing the attacks.

In the vagal type of syncope, where the symptoms are due to cardiac slowing or asystole, atropine by mouth in doses of 0.5 mg. ( $\frac{1}{120}$  grain) four times a day or ephedrine by mouth in doses of 30 mg. ( $\frac{1}{2}$  grain) three times a day will usually prevent the attacks. If the ephedrine causes nervousness or sleeplessness, the addition of 15 mg. ( $\frac{1}{4}$  grain) phenobarbital to each dose will suffice to prevent such symptoms. Ephedrine in the above dosage will prevent the depressor type of attack. The cerebral type does not respond to specific drug therapy. We have had good results in 9 of 11 such patients by surgical denervation of the most sensitive carotid sinus. The indications and technic for this procedure have been recently described by us. The operation should not be advocated except following prolonged observation and after other measures have failed, and only when the symptoms are severe enough to warrant such a major procedure.

Treatment for the acute attack is similar to that for vasovagal syncope: if the heart rate is slow or the blood pressure very low, 1 cc. of a 1: 10,000 solution of epinephrine should be administered intravenously.

**Dizziness and Syncope due to Stokes-Adams Attacks of Reflex Origin.**—The vagal type of carotid sinus syncope can be classified in this group and makes up by far the largest percentage of patients having transient attacks of reflex heart block. We have reported<sup>11, 14</sup> other types of reflex heart block in which the reflex was initiated in the eyeball (oculovagal reflex), esophagus, pharynx, larynx and bronchi (vago-vagal reflex) and produced attacks of heart block associated with dizziness and syncope. These attacks could be reproduced by irritation of the sensitive area and could be abolished with atropine.

As with the vagal type of carotid sinus syncope, the daily administration of atropine or ephedrine in the previously men-

tioned dosage will prevent such attacks. Treatment for the acute attack is similar to that for carotid sinus syncope.

**Other Types of Syncope.**—A comprehensive discussion of these types can be found elsewhere.<sup>11</sup> The treatment of such attacks is similar to that described for vasovagal syncope.

#### SUMMARY

In evaluating such symptoms as vertigo, giddiness and dizziness, it is important to determine whether they represent true vertigo or whether they represent sensations of a syncopal nature. There is a clear distinction between the two groups of sensations and they represent two separate and distinct syndromes, namely, true vertigo and syncopal attacks. The subjective symptoms of vertigo and those of syncope are each characteristic, regardless of the cause.

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## CLINIC OF DR. JACOB H. SWARTZ

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#### DISEASES OF THE SKIN

##### IMPETIGO CONTAGIOSA

**Definition.**—Impetigo contagiosa is a highly contagious condition of the skin caused by a streptococcus or staphylococcus or both.

**Clinical Picture.**—The primary lesion of impetigo is a vesicle varying in size from pinhead to the size of a quarter. Soon after the appearance of the lesion the vesicle may become pustular. It is usually situated on an inflammatory base. The lesions tend to flatten down with the formation of a crust which is usually the color of honey. The crusts last a few days, then they are thrown off and leave a red stain which fades gradually. The vesicles or pustules may remain discrete or coalesce and form various figures such as the figure of 8, etc., thus making it easily mistakable for ringworm of the skin (*tinea circinata*).

Impetigo can occur wherever there is an abrasion or may arise from insect bites, scratches, wounds, and intentional scratches due to itching. It is most commonly seen on the face and extremities although it may involve any other part of the body as well as the scalp.

**Etiology.**—Impetigo is much more common in children. It is highly contagious and auto-inoculable. It is spread from the original lesion by scratching and by careless technic in caring for it. The causative agent, as already mentioned above, is either streptococcus or staphylococcus organism or both. Impetigo contagiosa may complicate scabies, pediculosis capitis, or trauma.

**Differential Diagnosis.**—Impetigo involving the scalp should be differentiated from: (a) seborrhea capitis, (b)

# DIFFERENTIAL DIAGNOSIS HAIRY REGIONS

	Impetigo contagiosa.	Seborrhea capitis.	Psoriasis.	Tinea capitis.	Pemphigus.	Favus.
Primary lesion; vesicle, pustule, or bulla.	Present.	Absent.	Absent.	Absent.	Present.	Absent.
Involvement of hair sheath.	Absent.	Absent.	Absent.	Present.	Absent.	Present.
Honey-colored crust.	Present.	Absent.	Absent.	Absent.	Absent.	Absent.
Scutula.	Absent.	Absent.	Absent.	Absent.	Absent.	Present.
Alopecia.	Absent.	May be present.	Usually absent.	Present.	May be present.	Present.
Microscopic examination for fungus.	Negative.	Presence of bottle-shaped yeastlike organism.	Negative.	Positive.	Negative.	Positive.

# DIFFERENTIAL DIAGNOSIS NONHAIRY REGIONS

	Impetigo contagiosa.	Tinea circinata.	Bullous erythema multiforme.	Pustular eczema.	Pemphigus.
Primary lesion.	Vesicle, pustule, or bulla.	Pinpoint vesicle or macule.	Vesicle or bulla.	Papule and pustule.	Vesicle.
Honey-colored crust.	Present.	Absent.	Absent.	Usually absent.	Usually absent.
Duration.	Days to weeks.	Days to weeks.	Weeks.	Months to years.	Months to years.
Microscopic examination for fungus.	Negative.	Positive.	Negative.	Negative.	Negative.
Iris lesions.	Absent.	Absent.	May be present.	Absent.	Absent.
Psoriasis.	Absent.	Absent.	May be present.	May be present.	Present.
Mouth involvement.	Absent.	Absent.	Frequently present.	Absent.	May be present.

psoriasis, (c) tinea capitis, (d) pemphigus, (e) favus. Impetigo of the nonhairy regions should be differentiated particularly from: (a) tinea circinata, (b) erythema multiforme, (c) pustular eczema, (d) pemphigus. Impetigo of the bearded region should be differentiated particularly from sycosis vulgaris. (See differential diagnosis charts, p. 1628.)

**Treatment.**—Before treating a case of impetigo make sure of the contacts, *i. e.*, if there are any others in the family who have the same condition, otherwise the patient will reinfect himself. It is also important to make sure, if possible, whether the playmates have impetigo.

In the treatment of the impetiginous lesions we use the following lotion and salve:

R̄ Zinci oxidi ..	.....	5ij
Calamini ..	.....	5j
Phenolis ..	.....	5ss
Liquor calcis ..	.....	q.s. ad 5viij
M.		

Sig.—To be applied twice daily, morning and night.

R̄ Acidi salicylici ..	.....	5ss
Sulphuris praecipitatis ..	.....	5ss
Petrolati ..	.....	5j
M.		

Sig.—To be applied five minutes after using the lotion morning and night.

In those cases where only crusted lesions are present and in hairy regions the lotion is omitted and the ointment alone is used.

We advise against forcible removal of crusts. The parts involved should be washed with boric acid solution, using a separate piece of cheesecloth or cotton pad for each involved area. Wherever possible the lesions should be kept covered, especially in the case of a child. In the very extensive cases the use of ultraviolet rays aiming for an erythema dose in conjunction with the above-mentioned treatment is very helpful.

In cases of impetigo of the face or scalp be sure to examine for pediculosis capitis. If this condition is present treat as follows: pour 1 pint of carbolic acid (1:20) into a pitcher and add to it 1 pint of hot water, or use 1 tablespoonful of



95 per cent carbolic acid to 1 quart of hot water; tie a towel over the patient's eyes, place the patient's head over the basin and pour the carbolic acid solution (1: 40) over the hair; catch the solution in a basin and pour it back into the pitcher. Repeat the process until the hair is thoroughly soaked. Allow the hair to drip over the basin for a few seconds and then tie up the patient's head in a towel for one hour. To remove the nits which have been killed by the carbolic acid the hair should be combed, preferably with a wired comb known as a Derbac comb.

If the above method is not practicable in some instances, the following procedure may be used: the application of the following ointment nightly, followed by shampoo and fine combing in the morning. This is done until all evidence of nits has disappeared.

R̄ Acidi salicylici	.....	5ss
Sulphuris praecipitatis	.....	5ss
Petrolati	.....	5j
M.		

Be sure to rule out scabies as an underlying cause. If present, treat it.

#### IMPETIGO CONTAGIOSA OF THE NEWBORN

**Definition.**—This is a highly contagious skin condition appearing within the first few days of life and is caused by a streptococcus organism.

**Clinical Picture.**—The primary lesion is a vesicle or bulla, varying in size and number. These rupture easily, leaving bright red, moist, denuded areas. The chief location is in the folds of the axillae and groins, but may occur all over the trunk. This is a serious infection in the newborn.

**Treatment.**—If there are many areas and the body is extensively denuded, the child should be completely undressed and placed under a cradle that is heated by electric light bulbs. The bullae are cautiously ruptured, being careful not to allow the serum to run down to the normal skin by using a sterile cotton ball to collect the serum. Use a fresh cotton ball for each lesion. This is followed with the application of the following lotion:

R Zinci oxidi .....	ʒij
Calamini .....	ʒj
Phenolis .....	ʒss
Liquor calcis .....	q.s. ad ʒviij
M.	

Gentian violet (1 per cent aqueous solution) may be used in place of the above lotion.

**Precautions.**—1. Isolate the child at the first sign of a lesion.

2. Boil all equipment that is boilable. Discard and burn all other material.

3. The nurse should wear a gown when in contact with the patient. Hands should be thoroughly washed after handling patient.

4. In the case of breast-fed infants, it is advisable to pump the mother's breasts and feed the baby from a bottle.

#### ALOPECIA AREATA

**Definition.**—Alopecia areata is a disease of the scalp characterized by the presence of sharply defined patches of partial or complete baldness.

**Clinical Picture.**—The bald patches vary in size and configuration, and may be discrete or confluent. The skin is shiny and smooth, but not atrophic. Exclamation point hairs are found, particularly at the advancing border. The extent of involvement varies from one small patch to involvement of practically the entire scalp area.

In adult males the condition may be present over the bearded region.

Alopecia areata may become universal, involving the eyebrows, eyelashes, the axillary and pubic regions, as well as the rest of the trunk.

**Etiology.**—Cause unknown. *Theories:* (1) trophoneurotic; (2) endocrine disturbance; (3) parasitic; (4) dietary.

The trophoneurotic theory is based on the fact that cases have been reported following shock, anxiety, or worry. In rare cases the patches of alopecia follow a nerve area.

The endocrine theory is based on some good results obtained with the administration of thyroid.

The parasitic theory is based upon reported epidemics in institutions.

The diet deficiency theory is based upon cases reported improved when put on a high cystine diet.

Alopecia areata must be differentiated chiefly from luetic alopecia. (See chart below).

	Alopecia areata.	Luetic alopecia.
Circumscribed patches of baldness.	Present.	Absent.
Moth-eaten appearance.	Absent.	Present.
Exclamation point hairs.	Present.	Absent.
Other manifestations of lues.	Absent.	Usually present.
Serology.	Negative.	Positive.

**Treatment.**—1. Complete physical examination to rule out foci of infection. If present it is wise to eliminate them if possible.

2. Glandular therapy, thyroid or pituitary.

3. Sulphur treatment—taken either internally in the form of 5 grain tablets three times a day or collodial sulphur injections. Caution—watch for mucous colitis.

4. High cystine diet.

5. Local treatment is used with the purpose of producing local stimulation and hyperaemia.

(a) Potassium permanganate, 1 per cent, painted on morning and night.

(b) The following ointments may be used in place of the potassium permanganate:

℞ Acidi salicylici	
Sulphuris praecipitatis	āā ʒss
Petrolati . . . . .	ʒj
M.	

Sig.—Applied nightly.

℞ Phenolis	
Sulphuris sublimatis	āā ʒj
Naphtholis	ʒss
Cerae albae	ʒijj
Adipis	ʒv
M.	

(c) The Kromayer lamp to the affected parts, aiming for an erythema or vesiculation, and the air cooled lamp to the

trunk, aiming for a tonic dose. The general treatment is given about twice a week, while the treatment with the Kromayer lamp is repeated when the effects of the last treatment have disappeared.

### FUNGUS DISEASES OF THE SKIN

A fungus is a vegetable parasite which, if pathogenic, can attack skin, its appendages, such as hair and nails, mucous membrane, or the viscera. In this article a discussion of its pathogenicity as far as the skin and its appendages is in place.

**Classification of Fungi.**—Only a classification which can be applied to the clinical conditions to be discussed will be attempted. A strict botanical classification is too confusing and at present not most practical.

Group I. The myxomycetes.

Group II. Eumycetes.

The fungi pathogenic to man usually belong to Group II, which may be further subdivided as follows:

1. Phycomycetes. Reproduction by zygospores. Mycelium usually nonseptate and multinucleate.

2. Basidiomycetes. Reproduction by means of basidiospores. Mycelium septate.

3. Ascomycetes. Reproduction by means of ascospores. Mycelium is septate when present.

4. Hyphomycetes (Fungi imperfecti). Reproduction is by free borne spores (conidia). Ascus body absent. Mycelium septate. Complete sexual reproduction absent or unknown.

Fungi pathogenic to man belong chiefly to groups 3 and 4. For the sake of convenience to the clinician the above two groups may be further classified as follows:

(a) Yeasts and yeastlike organisms.

1. Saccharomycetaceae (true yeasts).

2. Cryptococcus (Torula).

3. Monilia.

4. Endomyces.

5. Coccidioidaceae.

(b) Ringworm fungi (Gymnoascaceae).

1. Microsporon

lanosum.

audouinii.

2. Achorion

quinckeanum.

schönleini.

## 3. Trichophyton

Ectotrichophyton, *e. g.*, *T. gypseum*.Megatrichophyton, *e. g.*, *T. rosaceum*.Favotrichophyton, *e. g.*, *T. ochraceum*;  
*T. violaceum*.

Eutrichophyton,

Neoendothrix, *e. g.*, *T. cerebriform*.Endothrix, *e. g.*, *T. crateriforme*; *T. acuminatum*.

## 4. Epidermophyton

The organisms which cause sporotrichosis and actinomycosis belong to the Fungi imperfecti.

**Diagnosis.**—In addition to the clinical characteristics laboratory data is essential for the correct diagnosis of fungus infection. The simplest method is the *direct microscopic examination* of the material suspected.

**Technic.**—1. Select the proper material for examination, since many negative findings are due to selecting the material in a hit or miss manner. In tinea capitis or favus select the stumps of hairs; in tinea barbae examine the hairs in pustules or nodules as well as the seropurulent material; in blastomycosis and sporotrichosis examine the fluid in the nodules and abscesses; in tinea of the glabrous skin such as tinea circinata, tinea cruris epidermomycosis of the hands or feet, the skin scales from the roofs of fresh vesicles are to be taken for examination.

2. Place some of the material between two slides which can be held together by elastic bands, label and put away for cultural purposes. The remaining material is used for microscopic examination.

(a) Unstained preparation: place the scales on a slide and add a few drops of potassium or sodium hydroxide (30–40 per cent). Put on cover slip and heat gently. Allow it to stand for ten to fifteen minutes for clearing and then examine with microscope.

(b) Stained preparation: place the scale on a slide and add a few drops of 5–10 per cent of potassium hydroxide and heat slightly. Wash scale in water for two to three minutes, using a watch crystal. Put scale back on slide and add a drop of  $\frac{1}{2}$  per cent lactophenol cotton blue, put on cover glass and heat slightly. In case of thick scales or nail preparation a 1 per cent alcoholic solution of cotton blue is used and the preparation is mounted in clear lactophenol.

## TINEA CAPITIS (RINGWORM OF THE SCALP)

This is a disease of the scalp caused by different species of vegetable parasites. It is a disease of childhood chiefly and is highly contagious.

**Clinical Picture.**—The following are the most characteristic findings: (1) scaliness; (2) broken off hairs covered with a grayish sheath; (3) prominent hair follicles; (4) partial baldness; (5) in some instances the follicular openings stand out as large black dots.

All or part of the above findings may be noted. The patches may be discrete and scattered, varying in size, or they may coalesce to involve almost the entire scalp. Involvement of adjacent nonhairy skin may be noted, particularly when the offending organism is of the large spore variety.

**Etiology.**—The condition is most common in children under puberty, although scattered reports of occurrences in adults are present. The causative agent is a vegetable parasite either of the large or small spore variety. In this part of the country the *microsporon lanosum* is the more common offending agent.

**Sources of Infection.**—(1) Pet animal, (2) contact with infected child, (3) interchanging of caps, and (4) combs and brushes.

## DIFFERENTIAL DIAGNOSIS

	Tinea capitis.	Impetigo.	Seborrhea capitis.	Favus.	Psoriasis.
Broken off hairs covered with a grayish sheath.	Present.	Absent.	Absent.	Absent.	Absent.
Silvery scale.	Absent.	Absent.	Absent.	Absent.	Present.
Scutula.	Absent.	Absent.	Absent.	Present.	Absent.
Atrophy	Absent.	Absent.	Absent.	Present.	Absent.
Honey-colored crusts on nonhairy regions	Absent.	Present.	Absent.	Absent.	Absent.
Greasy yellowish scale.	Absent.	Absent.	Present.	Absent.	Absent.
Age of incidence	Under puberty.	Usually children.	All ages but more common in adults.	All ages.	Usually young adults.
Microscopic examination for fungus	Positive	Negative.	Negative.	Positive.	Negative.

## KERION

This is a purulent type of lesion simulating a large abscess or carbuncle and most often seen in children.

**Clinical Picture.**—(1) Partial alopecia; (2) inflammation; (3) edema and boggiess; (4) a carbuncle-like tumor which discharges a mucoid or mucopurulent secretion.

Pain may or may not be present. Microscopic examination of the secretion or the involved hairs shows the presence of a large spored ringworm. Caution: this condition must not be mistaken for boils or carbuncles, because incision may cause a spread of the disease.

**Treatment.**—The disease responds well to treatment, which consists of a daily shampoo of soap and water, followed by the application of a mild fungicidal ointment such as

R. Acidi salicylici . . . . .	5ss
Sulphuris præcipitatis . . . . .	5ss
Petrolati . . . . .	5j
M.	

The child should not be allowed to attend school until the condition is cured. Boilable caps must be worn. (See *Tinea Capitis*).

#### TINEA FAVOSA

This disease is caused by a vegetable parasite known as *Achorion schönleinii* and may involve the skin, nails, or scalp, particularly the last.

**Clinical Picture.**—The following characteristics are usually found in favus involving the scalp. (1) *Scutula*. These are yellow cup-shaped crusts which are more commonly found at the periphery of the involved areas and resemble small mushrooms. (2) Brittleness and loss of hair. (3) Atrophy and loss of hair. (4) Offensive odor which may be compared with that of the urine of mice.

**Differential Diagnosis.**—See *tinea capitis*.

**Etiology.**—This disease is caused by a vegetable parasite known as the *Achorion schönleinii*. It attacks both sexes and may occur at any age.

**Modes of Transmission.**—(1) Direct contact with an individual afflicted with the disease; (2) pet animal, particularly cat; (3) contaminated articles, particularly cap, brush or comb.

**Treatment of *Tinea Capitis* and *Tinea Favosa*.**—Since the infection involves the hair, the logical procedure is to get

rid of the infected hairs by one of the following procedures: (a) manual epilation; (b) x-ray epilation, or (c) epilation with thalium acetate.

Manual epilation can be accomplished by plucking out the infected hairs by means of an epilating forceps, or by stripping the affected areas after the application of adhesive plaster. It is advisable to cut the hairs short or even shave them in order to find the exact extent of the involvement. The manual epilation should be done daily in order to be effective. The infected hairs which have been removed should be collected in a paper bag and then burned. Following the epilation an application of the following lotion should be made on two successive days and the ointment on the third day:

℞ Phenolis	
Camphorae	āā ʒj
Iodine	ʒj
M.	

℞ Acidi salicylici	
Sulphuris praecipitatis	āā ʒss
Petrolati	ʒj
M.	

The following ointment may be used daily instead of the above combination:

℞ Sulphuris sublimati	ʒj
Phenolis	ʒj
Naphtholis	ʒss
Cerae albae	ʒiij
Adipis	ʒv
M.	

*Ethyl Iodide Inhalation.*—This method of treatment was originated by Swartz, Blumgart, and Altschule and is as follows: by means of a special inhalation apparatus ethyl iodide is inhaled on two successive days and omitted on the third day. The dose begins with 1½ cc. (3 Gm.) and is increased ½ cc. (1 Gm.) per dose until 4 cc. (8 Gm.) is reached. The dose for children is one half of the above mentioned. (For further information see treatment of epidermophytosis).

*x-Ray Epilation.*—This method of treatment is risky except in the hands of experts since the margin of safety is narrow and permanent epilation may result (for technic see



McKee's book on "x-Ray Treatment of the Skin" or other standard textbooks on dermatology). Caution: no irritating or stimulating ointments should be used for at least ten days prior to x-ray treatment and for two weeks after the treatment.

*Thallium Acetate*.—This drug is known to cause a temporary epilation but is rather dangerous in the hands of the inexperienced, as it has been known to produce fatalities. Its action is chiefly on the sympathetic nervous system. The dosage is 8 mg. per kilogram of body weight and it is dissolved in sweetened water made up as follows: 1 teaspoonful of sugar to 100 cc. of water. The treatment should not be repeated within three months. The first signs of epilation are usually noticed two weeks after the administration of the drug. The local treatment is the same as above.

**Prophylaxis.**—(1) If pet animal is found to be the causative agent it should be sent to an animal hospital for treatment or disposal; (2) epilated infected hairs must be collected in paper bag and burned; (3) sterilize by boiling the clippers and other utensils after using; (4) wear boilable stocking caps. These should be boiled for twenty minutes after using; (5) all outside caps that have been worn should be burned; (6) the child should not be allowed to attend school until three successive negative weekly microscopic examinations have been obtained.

#### TINEA BARBAE (TINEA SYCOSIS; RINGWORM OF THE BEARD)

**Definition.**—This disease is an infection of the hairs in the bearded region caused by a vegetable parasite, chiefly of the large spore variety.

#### DIFFERENTIAL DIAGNOSIS

	Tinea barbae.	Sycosis vulgaris.
Distribution.	Common in the mandibular and submaxillary regions, rarely on the upper lip.	Beard and upper lip.
Primary lesion.	Nodule with tendency to abscess formation.	Follicular pustule or papule.
Microscopic examination for fungus.	Positive.	Negative.

**Clinical Picture.**—The chief characteristics are: (1) hairs that are loose and broken off; (2) partial alopecia; (3) nodular abscesses resembling kerion; (4) location is chiefly mandibular or submaxillary regions; practically never involves the upper lip. The condition is rather rare.

**Treatment.**—(1) *Epilation.*—(a) Manual epilation in conjunction with local application as in tinea capitis; (b) x-ray epilation (for technic refer to McKee's textbook on "x-Ray Treatment of the Skin" or Andrew's book on Dermatology); the x-ray treatments have also beneficial action upon the accompanying inflammatory tissue.

(2) *Shaving Precautions.*—(a) Omit shaving brush as it cannot be sterilized by boiling; (b) new blade for each shave; (c) sterilize blade holder by boiling or by keeping in alcohol overnight; (d) do not shave too close; (e) shave uninvolved areas first and leave involved areas for last. The electric shaver has been found to be less irritating than the average razor.

#### TINEA CIRCINATA

Tinea circinata is a highly contagious disease of the glabrous skin characterized by the presence of circinate erythematous lesions with a border made up of minute vesicles. The disease is more common in children.

#### DIFFERENTIAL DIAGNOSIS

	Tinea circinata.	Impetigo contagiosa.	Syphilis.	Eczema.
Sharply defined border	Present.	May be present.	May be present.	Usually absent.
Circinate lesions.	Present.	May be present.	May be present.	Usually absent.
Vesiculation at border	Present.	May be present.	Absent.	May be present.
Clearing center	Present.	May be present.	May be present.	Usually absent.
History of contagion	Present.	Present.	Present in early stages.	Absent.
Honey-colored crust	Absent.	Present.	Absent.	Absent except in impetiginous eczema.
Serology	Negative.	Negative.	Positive.	Negative.
Microscopic examination for fungus	Positive.	Negative.	Negative.	Negative.

**Clinical Picture.**—This disease presents the following characteristics: (1) circinate erythematous lesions

varying in size. Some of the lesions may even resemble the figure 8 or form a circle within a circle; (2) a border consisting of minute vesicles and crusting; (3) tendency toward clearing in the center; (4) absence of atrophy or scarring; (5) usually found on the face or neck, but may be found on any part of the trunk or extremities.

**Modes of Transmission.**—(1) Direct contact with individual that has the disease; (2) pet animal (cat or dog); (3) contaminated clothing, etc.

**Treatment.**—Since the condition is contagious, the child should not be allowed to attend school. Be sure to locate, if possible, the source of infection.

Locally the lesions are washed separately, using a separate piece of gauze for each area, and a fungicidal ointment such as listed below is applied morning and night. The disease responds readily to treatment.

℞ Acidi salicylici	
Sulphuris praecipitatis	āā ʒss
Petrolati	ʒj
M.	

#### CRYPTOCOCCOSIS EPIDERMICA

This condition was described by Dr. C. J. White and Dr. J. H. Swartz in 1928. The disease affects the female sex largely, may appear at any age and last indefinitely if untreated. It usually begins on the eyelids, particularly the upper, and may spread to the flexures of the elbows, thighs and popliteal spaces. The lesions are polymorphous, chiefly macular and infiltrative, but never moist unless secondarily infected with bacteria. In the early stages the lesions have a café-au-lait color, but later may become lichenified and even pigmented. The organism found on direct microscopic examination of the scales is a budding yeast of the cryptococcus family. The chief symptom is itching, at times severe.

**Treatment.**—(1) Clothes that can be washed and boiled should be worn next to the skin; (2) a superfatted soap for bathing purposes; (3) the following ointment should be applied one or two times daily to all involved parts except eyelids:

R Mercurochrome crystals .....	gr. x
Aquae .....	℥ xx
Acidi salicylici .....	ʒss
Petrolati .....	
Lanolini aa .....	q.s. ad ʒj
M.	

(4) In some cases fractional doses of x-ray is helpful. The following ointment is advised in conjunction with the x-ray treatment:

R Mentholis ..	gr. $\frac{1}{4}$ -1
Zinci oxidi .....	ʒss
Amyli .....	ʒij
Petrolati ..	ʒj
M.	

(5) Ethyl iodide inhalation. This is used in the more extensive cases. (See epidermophytosis.)

#### EPIDERMOPHYTOSIS (DERMATOMYCOSIS, ECZEMA MYCOTICUM)

This condition is caused by a variety of vegetable parasites and resulting in various clinical pictures dependent upon the location. Four types are particularly known, although others have been described.

**Clinical Types.**—1. The *erythematous*—more commonly found in the folds such as the groins, perineum, axillae, and under the breast in females. The lesions are usually sharply demarcated with maceration in the fold and a slightly elevated border, frequently made up of pinpoint vesicles. In long-standing cases one may also note lichenification and pigmentation; the latter is particularly present in brunettes and in those with tendency to pigment.

2. The *vesicular type* occurs chiefly on the palms, plantar aspects, and interdigital spaces. The vesicles are intradermal, resembling sago grains, and when drying up turn brownish in color. Occasionally one may even note bullae. Secondary infection with resulting pustulation is not uncommon. In addition, there is scaling, maceration, crusting and fissuring. Lymphangitis and lymphadenitis may accompany this condition, especially when the infection involves the feet.

3. *Hyperkeratotic Type.*—Epidermophytosis is inclined to hypertrophy in regions in which the stratum corneum is nor-

mally abundant. On the palms hyperkeratosis is relatively mild but common; on the soles it is decidedly emphasized and still more frequent. The color of the lesions is usually yellow or more often a striking orange. The more common locations are the inner side of the big toe, the ball of the foot and the heel. Fissuring frequently accompanies this condition.

4. The *macerated form* has its predilection in the webs of the fingers and of the toes, the intergluteal fold, the contact points of the penis and scrotum, and the submammary folds. This form occurs particularly in association with the above described erythematous type, especially in the folds of the skin.

5. The combination of any of the above four types with one type predominating is not infrequently seen.

**Treatment.**—The results in the treatment of epidermophytosis at best is not most satisfactory but with the patient's cooperation and a definite understanding of the pathology by the physician, one can frequently obtain gratifying results.

The following are some of the fungicidal preparations used: chrysarobin, iodine, thymol, oil of cinnamon, potassium permanganate, copper sulphate, gentian violet, mercurochrome, sodium hyposulphite, sulphur, benzoic acid and salicylic acid. A keratolytic agent is necessary in combination with the fungicidal preparation in order to obtain results. Salicylic acid in strengths from 3 to 6 per cent is most frequently used.

The following are some of the fungicidal ointments advised:

R	Iodine crystals	gr. v-x
	KI enough to dissolve the iodine	
	Acidi salicylici	ʒss
	Lanolini	
	Petrolati āā	q.s. ad ʒj
	M.	

The iodine and its solvent may be omitted or it may be replaced by 1 per cent thymol or 3 per cent chrysarobin.

R	Acidi salicylici	gr. xv
	Acidi benzoici	gr. xxv
	Paraffini mollis	ʒij
	Olei cocois nuciferae	q.s. ad ʒj
	M.	

R Mercurochrome crystals .....	gr. x-xx
Aquae .....	m xx
Acidi salicylici .....	ōss
Petrolati .....	
Lanolini āā .....	q.s. ad 3j
M.	

Particularly useful in the vesicular type.

In all instances it is wise to precede the application of the ointment by a soaking of the hands or feet in warm saturated solution of boric acid or potassium permanganate,  $\frac{1}{20}$  to 1 per cent solution.

In the severe cases the soaks and applications are made morning and night. In order to protect the bed linen the patient is advised to wear old cotton stockings on the feet (use a woman's stocking, cut out the heel and cut down the leg part to make two ties and fasten about the ankle to hold the dressing in position). The patient should also wear cotton gloves on the hands. In the milder types, the patient is told to soak the affected parts morning and night, but the ointment is applied only at night. In the morning he is to dust a powder between the toes. Boilable socks must be worn.

The following powder is useful as a prophylaxis in epidermophytosis of the feet:

R Acidi salicylici .....	2
Acidi benzoici .....	2
Talc .....	30

Caution: beware overstimulating and strong applications in the acute stages. It will only serve to aggravate and spread the condition.

**Treatment of Shoes.**—Soak paper towels in formalin, being careful to protect the hands; stuff the soaked papers into the shoes and slippers. Place in a large paper bag, tie with a string and put into the closet for twelve hours. Remove the paper and place the shoes and slippers out in the sun for at least twenty-four hours to air before wearing them.

**Ethyl Iodide Inhalations.**—In the acute vesicular cases, in the cases with an accompanying epidermophytide or trichophytide, and in stubborn cases of long standing, the administration of ethyl iodide by means of inhalation is advised.

**Technic.**—The inhaler devised by Swartz, Blumgart, and

Altschule is used. This inhaler is so devised that a comfortable mixture of ethyl iodide and air is inhaled by the patient. Dosage: begin with  $1\frac{1}{2}$  cc. (3 Gm.) of ethyl iodide and increase  $\frac{1}{2}$  cc. (1 Gm.) per dose until a total of 4 cc. (8 Gm.) is reached. Continue with 4 cc. Inhalations are given on two successive days and omitted on the third day until marked improvement is noted, when the treatment is administered less and less frequently.

Caution: (1) Do not administer ethyl iodide to patients suffering from pulmonary tuberculosis or nephritis; (2) watch for an iodide rash. If present, omit treatment till eruption disappears and then start gradually; (3) watch for peripheral neuritis. This is a rare complication. If noted, omit treatment and do not attempt inhalations again.

**Prophylaxis.**—The rules to be observed are: (1) Do not walk around with bare feet; (2) do not wear anyone's slippers or shoes; (3) wear rubber slippers or place a towel on the shower-bath floor; (4) wash feet at least once a day with soap and water. Dry thoroughly but gently; (5) apply powder mentioned in the discussion of treatment; (6) treat shoes as advised in discussion of treatment if there is any question of contamination.

The treatment with trichophytin injections has not proved most successful in the author's hands. However, the development of autogenous vaccines might prove to be valuable.

#### EPIDERMOPHYTIDE OR TRICHOPHYTIDE

In addition to the direct infection one may see a toxic or allergic eruption which is symmetrical and which is commonly seen on the extremities, particularly the upper, and may be macular, papular, or vesicular in character. It may also be follicular, lichenified, or squamous. On microscopic examination one never finds the fungus in the skin scrapings from these lesions.

#### EROSIO INTERDIGITALIS

This condition is more frequently seen in housewives and dishwashers. It is caused by a yeastlike organism belonging to the monilia family. The infection usually attacks the cleft of the middle and ring fingers or that of the middle and fore-

fingers of one or both hands; sometimes, though not often, two interspaces of one hand may be involved. The affected area is dirty white, soft from edema, sharply defined, and the border is frequently red and angry.

**Treatment.**—1. Hands must be protected from the dish water either by wearing white cotton gloves and thin rubber gloves over them or by washing dishes in such a way as to avoid getting the dish water on the hands.

2. *Local treatment:*

R̄ Mercurochrome crystals . . . . .	gr. x
Aquae . . . . .	℥ xx
Acidi salicylici . . . . .	ʒss
Petrolati . . . . .	
Lanolini āā . . . . .	q.s. ad ʒj
M.	

Sig.—To be applied morning and night.

Cleanse the involved areas with a saturated solution of boric acid.

R̄ Mild mercurous chlorid . . . . .	gr. xxx
Lime water . . . . .	q.s. ad ʒviii
M.	

Apply with gauze moistened in this solution and allow it to stay in each involved area for five to ten minutes. Do this about three times daily.

Between the applications a drying antiseptic powder should be dusted on frequently.

### TINEA VERSICOLOR

**Definition.**—An eruption of the skin involving particularly the upper trunk and caused by a vegetable parasite known as the *microsporon furfur*.

**Clinical Picture.**—The lesions are macular in type, varying in size from pinhead to large patches when coalescence takes place. The color varies from the most delicate buff to a reddish deep brown, or even blackish hue. The macules are covered with a furfuraceous scale which on direct microscopic examination reveals the presence of spores and hyphae. The upper trunk is chiefly involved but it may extend to axillae, abdomen, and groins.

**Etiology.**—The disease is caused by a vegetable parasite known as the *microsporon furfur* and first described by Eichstedt in 1846. It is not easily transmitted but members of one family have been known to communicate the disease occasionally to one another. This organism which is so easily



demonstrated on direct microscopic examination of the skin scales has not been successfully cultivated.

**Treatment.**—1. Daily hot bath followed by the application of sodium hyposulphite (25 per cent solution) or the following ointment:

R̄ Acidi salicylici	
Sulphuris praecipitatis	āā 5ss
Petrolati	5j
M.	

2. Ultraviolet light aiming for erythema doses.

No matter what type of treatment is used, care must be taken to boil the underclothing or wash and press with a hot iron.

### BLASTOMYCOSIS

Blastomycosis may be either primary or secondary to some deeper infection of the viscera or bony structure. Only primary blastomycosis will be discussed here.

**Clinical Picture.**—Cutaneous blastomycosis is known to produce granulomatous lesions which progress slowly and are warty in character and show multiple discharging sinuses. The lesions are often multiple and are most frequently seen on exposed parts, although they may occur on any part of the integument. The lesions when present on the hands and feet show a greater tendency to papillomatous formation. The lesions are usually covered with a thick dirty gray or brown crust which, on removal, shows exuberant granulations covered with seropurulent exudate. The discharge is found to come from multiple sinuses which communicate with multiple subcutaneous abscesses. The lesions show a tendency to central involution with scar formation. Frequently the lesions simulate tuberculosis verrucosa cutis and can only be differentiated from it by histological and mycological studies.

**Etiology.**—The family of organisms causing blastomycosis belong in the yeastlike family and fungi imperfecti. The belief that one individual organism is responsible for all cases of blastomycosis is not accepted by most mycologists. It is generally accepted that there are a plurality of species of the fungi causing this disease.

**Treatment.**—(1) Surgery or surgical diathermy; (2)

x-ray treatment; (3) massive doses of iodides by mouth, intravenously, or by inhalation of ethyl iodide; (4) a combination of any or all of the above methods.

### SPOROTRICHOSIS

**Definition.**—Sporotrichosis of the skin is a subacute or chronic infectious disease due to one of several species of vegetable parasites of the genus *sporotrichum* and characterized by the presence of subcutaneous nodules which tend to follow lymphatic distribution. This variety is the most common in America. Other varieties have been described, but because of the rarity, will not be considered here.

**Clinical Picture of Lymphangitic Sporotrichosis.**—The primary sore which is a nodule or ulcer usually follows trauma and appears at the point of inoculation. The lesions that follow are multiple subcutaneous painless nodules which soften and break down. An ascending lymphangitis may accompany the nodules. This is characterized by a painless, cordlike thickening of the lymphatic vessels.

**Treatment.**—Iodine is the drug of choice given orally, intravenously or by inhalation (ethyl iodide). Some recommend x-ray therapy either alone or in conjunction with iodides. Iodine ointment to the lesions is helpful. Surgery is contra-indicated.

### CHRONIC PARONYCHIA

**Definition.**—Chronic paronychia is an infection of the nail and surrounding soft tissue caused by a pathogenic yeast, usually a monilia.

**Clinical Picture.**—The outstanding characteristics are: (1) A thickening and inflammation of the soft tissue about the nail; (2) grooving and partial destruction of the nail, particularly at the lateral border and at the base. Any nail may be involved. In association with this condition one frequently finds an *erosio interdigitalis* (described above). Both conditions are found particularly in domestic servants, housewives, and dish washers. The starting point is probably trauma from the excessive use of warm water. This is later followed by a superimposed yeast infection from contact with fruits, vegetables and dish water. The cocci may produce a

picture simulating the one just described, and might necessitate laboratory studies to differentiate.

**Treatment.**—(Same as for Erosio Interdigitalis).

# ONYCHOMYCOSIS (TINEA UNGUIUM, RINGWORM OF THE NAIL)

**Definition.**—Onychomycosis is an infection of the nail caused by a vegetable parasite.

**Clinical Picture.**—The involved nail is brittle, discolored yellowish brown or darker, lusterless and hypertrophic. One or all of the nails of the hands and feet may be involved. It may accompany fungus infection of the skin or it may be the sole finding. The nail bed and the lateral aspects of the finger nails are chiefly involved. Beneath the involved parts, particularly the lateral margins, are accumulations of soft débris. Involvement of the soft tissue about the nails may or may not be present. The condition is rather persistent and resistant to treatment.

## DIFFERENTIAL DIAGNOSIS

	Onycho- mycosis.	Lues.	Psoriasis.	Dystrophy.
Pitting and stippling.	Absent.	Absent.	Present.	Absent.
Yellowish-brown discoloration.	Present.	Absent.	May be present.	Absent.
Other psoriatic lesions.	Absent.	Absent.	Usually present.	Absent.
Other manifestations of lues.	Absent.	Usually present.	Absent.	Absent.
Other manifestations of trophic disturbances.	Absent.	Absent.	Absent.	Usually present.
Serology.	Negative.	Positive.	Negative.	Negative.
Microscopic examination for fungus.	Positive.	Negative.	Negative.	Negative.

**Treatment.**—(1) *Local Treatment.*—(a) Warm boric acid solution soaks for fifteen minutes twice daily; (b) scrape the involved nails with the rough side of a broken slide or with a knife until it hurts; (c) apply one of the following ointments:

R Acidi salicylici  
Acidi benzoici  
Adipis  
M

℥ss  
ʒj  
ʒj

R̄	Mercurochrome crystals	gr. x
	Aquae	℥ xx
	Acidi salicylici	ʒss
	Lanolini	
	Petrolati āā	q.s. ad ʒj
	M.	

Sodium perborate paste may be used in place of the above salves. A few drops of water are added to sodium perborate powder to make a paste. This is applied to the fingernail and nail bed and covered with a rubber finger cot and allowed to stay on overnight. It is helpful to soak the nails in a warm saturated solution of boric acid before applying the paste.

2. *x*-Ray treatment.

3. Surgery in combination with above mentioned local treatment.

4. Ethyl iodide inhalations.

### ERYTHRASMA

This condition is not common in temperate climates but it is seen often enough to merit some consideration. It is characterized by brownish, slightly scaly, fairly demarcated superficial patches involving chiefly the axillae and groins. It is only mildly infectious, and is caused by a *Microsporon minutissimum* which can be demonstrated by direct microscopic examination of the scales.

**Treatment.**—Sodium hyposulphite, 25 per cent solution, applied nightly until all signs of the condition disappear or

R̄	Acidi salicylici	
	Sulphuris praecipitatis	āā ʒss
	Petrolati	ʒj
	M.	

SIG.—Apply nightly until all signs of activity have disappeared.



## CLINIC OF DR. CHESTER M. JONES

MASSACHUSETTS GENERAL HOSPITAL

### THE TREATMENT OF JAUNDICE AND HEPATIC INSUFFICIENCY

THE success of medical treatment of disease of the liver depends in large part upon a proper understanding of the physiological significance of hepatic insufficiency. Few of the many functions of the liver are accurately understood, but there is a sufficient amount of information regarding them to enable one to obtain a fairly clear clinical understanding of the processes involved in hepatic failure. Regardless of the type of liver disease, whether it be due to acute infection or to a specific toxin, the problem is always one of a restoration of certain specific phases of liver function. Of these the best understood is that related to sugar metabolism and glycogen deposition. Next in importance is the detoxification of various poisonous substances, bacterial or otherwise, deamination of amino acids, the maintenance of serum protein, particularly through the formation of fibrinogen, the control of normal blood coagulation, participation in the formation of hemoglobin, the control of body fluids through an adequate portal circulation and maintenance of serum protein, the excretion of bile and the formation of bile acids, and the elimination of foreign substances. When these functions are disturbed certain symptoms may appear which properly may be ascribed to these various phases of hepatic insufficiency. Improper handling of carbohydrate probably accounts for the marked weakness and occasional fainting attacks in acute liver disease. The anemia is undoubtedly the result of the failure of the liver to aid in the formation of hemoglobin and in the maturation of red cells as well as to the presence of spontaneous hemorrhages from mucous membranes. The occur-

rence of edema and ascites in association with oliguria obviously is due to a breakdown in the normal control of body fluids in their relation to serum protein, liver glycogen, and portal flow. Jaundice results from the inability of the liver to excrete bilirubin and the lack of proper fat absorption from the digestive tract is intimately associated with the inadequate supply of bile acids to the bowel. Failure of the liver to excrete foreign substances at least provides an opportunity for measuring one of the liver functions, namely, the ability of the liver to excrete dye such as bromsulphalein or rose bengal and permits us to measure liver efficiency to a certain extent. The toxemia that is so frequently present in severe liver disease may be due to a combination of many of the above factors and may be associated with such varying symptoms as drowsiness, nausea, vomiting, and purpura. Acidosis may occur either in the form of a ketosis due to starvation or because of an excessive amount of amino acids in the blood with a resulting diminution of the normal alkali reserve.

If one is to treat the symptoms enumerated above and to attempt to restore to a normal level the hepatic functions which they represent to a greater or lesser extent, one must employ certain specific measures. These are, in the order of importance, complete rest, removal of any specific poison such as alcohol, cinchophen, etc., an adequate supply of simple carbohydrate and a minimal amount of fat, moderate limitation of fluid intake, a diet that contains at least a maintenance ration of protein, transfusion as needed to combat anemia and spontaneous hemorrhage, aided by adequate amounts of iron, diuretics, and possibly alkali at times to combat an existing acidosis. The principles of such treatment have been more or less generally recognized for some years, but failure to successfully treat individual cases of severe liver disease may frequently be laid to the fact that the treatment did not include a sufficient consideration of all the above factors. It is true, however, that in the past few years cases which were given up as hopeless frequently have been successfully treated with a resulting restoration of almost normal function.

The following cases are presented in brief detail as examples of adequate and successful treatment in patients suffering from serious hepatic failure.

The first case is that of an emotionally unstable woman of thirty-nine who had had no symptoms prior to five years before admission to the hospital. At the beginning of this period she began to consume gradually increasing amounts of alcohol, finally taking about  $\frac{1}{2}$  pint daily. She was habitually constipated until two years before admission at which time her bowel movements became more regular and less constipated. She had had an increasing number of digestive symptoms during this period consisting of anorexia, gas, nausea and finally vomiting. These symptoms had all increased strikingly in the year preceding admission to the hospital. Eight months before admission she noticed that her clothes were apparently too tight, as if her abdomen were becoming larger. Five months later the patient's sister noticed that her eyes were becoming yellow and associated with this there was noticeable swelling of the feet without fatigue, dyspnea, cardiac, or urinary symptoms. There was no abdominal pain at any time. During the few weeks before admission her bowel movements had become light in color. In spite of the apparent increase in the size of her abdomen she had lost 36 pounds in the last year of her present illness. Just prior to admission she consulted a doctor who told her she had a slight elevation of temperature. The history was otherwise negative.

On admission her physical examination revealed a good deal of emaciation of her arms, face, and thorax. There were spider telangiectases over the face and thorax. The veins in the epigastrium were dilated. Sclerae and skin were jaundiced. Abdomen was large with some herniation of the umbilicus and there was shifting dullness. The liver edge was easily felt about a finger-breadth below the costal margin. The spleen was not palpable. There was edema of the vulva, legs and feet. There was marked hyperesthesia of the feet and general tumor of the hands. Mentally she was definitely disoriented and on admission had a temperature of  $101^{\circ}$  F.

Laboratory data on admission were as follows: urine negative except for large amount of bile, stool light brown in color with no occult blood. Red count 3,520,000, hemoglobin 70 Tallqvist (?). White count 18,000. Differential not remarkable. The red cells showed slight achromia and polychromatophilia with some variation in size and shape. Hinton was negative. Icteric index 40. Quantitative van den Bergh 15 mg. per 100 cc. Serum protein 5 per cent.

It was felt that the patient was suffering from hepatic insufficiency, probably in the nature of a subacute yellow atrophy superimposed on an alcoholic cirrhosis. Treatment was outlined as follows: complete rest in bed, avoidance of alcohol, a diet consisting of high carbohydrate, low fat, maintenance of protein. Intravenous glucose therapy was instituted and the patient was given 2000 cc. 10 per cent glucose in normal saline solution.

During the first few days in the hospital the patient was extremely irrational and had a typical Korsakoff syndrome. Mental symptoms were controlled with paraldehyde and subsided after three or four days. The jaundice definitely increased during the first three weeks, reaching a peak at this time with a quantitative van den Bergh of 25 mg. per 100 cc. At the same time there was a very definite increase in the amount of abdominal fluid and the patient became rather stuporous and unable to eat except in very small amounts. Olicuria was striking during the second week of the hospital stay, the patient putting out only 10 to 20 ounces of urine a day during this period. Ten days after admission she weighed 138 pounds, or 10 pounds more than when she entered the hospital. Because practically all the veins were thrombosed it was necessary to discontinue the intravenous glucose therapy at this time.



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On the tenth day abdominal paracentesis was performed and 3000 cc. of straw-colored fluid was withdrawn, specific gravity 1.011 but otherwise not remarkable. The following day 1 cc. of salyrgan was given intraperitoneally without effect. A day later because of the patient's very poor condition and the fact that her anemia seemed to play an important part in her condition she was transfused with 600 cc. of blood and was again transfused six days later with the same amount. Salyrgan was again administered the second day after the transfusion with a moderate diuresis but following this there was a return of oliguria and a gradual rise in temperature until it reached 103° F. after five days. At this time the patient was so ill the second transfusion was performed and this was followed by a third injection of 2 cc. of salyrgan without any appreciable result. Two days later, or three weeks after admission, a second abdominal paracentesis was done with withdrawal of 4300 cc. of fluid of the same character as that obtained the first time. A third tap was performed five days later at which time 4000 cc. of fluid were removed. Following the second paracentesis the spleen was easily felt and continued to be palpable throughout the remainder of the acute illness. Following the second transfusion the patient's appearance was distinctly improved and along with a slight drop in temperature her symptoms of anorexia, nausea, and vomiting began to subside. Coincidentally, the stools which had been clay-colored began to return to a normal color and the jaundice diminished so that four days later the van den Bergh had dropped to 20 mg. per 100 cc. Improvement was gradual from this point on, the jaundice diminishing and the van den Bergh dropping to 7 mg. per 100 cc. one month after admission, at which time the patient was putting out a slightly greater amount of urine. A fourth and final paracentesis was performed almost five weeks after admission, at which time 4 liters of fluid were removed. On the same day 2 cc. of salyrgan were given intramuscularly with a very excellent diuresis, the first that had been obtained. Eight days later a final intramuscular injection of 2 cc. salyrgan was administered, this time resulting in a diuresis which lasted for three days with a loss of 4 pounds in weight. At this time the patient was practically symptom-free, was eating well and had improved mentally to such an extent that she was essentially normal.

She was discharged from the hospital seven weeks after admission with no evidence of ascites and very slight jaundice. The urine was free from bile and the stools were normal in color. The subsequent course of the case indicated that there was a very definite underlying cirrhosis which was also borne out by the finding of a positive Takata-Ara test.

This case illustrates well the various measures which can be employed successfully in a case of extreme hepatic insufficiency. The failure of liver function was evidenced by jaundice, drowsiness, nausea, vomiting, oliguria, edema, ascites and anemia. The specific measures which were employed were the administration of adequate amounts of carbohydrate by mouth and vein, relative limitation of fluids, complete rest, removal of the toxic substances that caused hepatic insufficiency, in this instance alcohol, the use of diuretics, transfusion, and subsequently, large doses of iron.

Two points are of interest. The first was that the patient

did not begin to improve until after two transfusions, which apparently brought about clinical improvement as well as an immediate rise in the red count. The other point of interest lies in the fact that a diuresis occurred at about the time when the patient's liver began to function more efficiently. In this instance it was apparently produced by the use of salyrgan, although only after the drug had been given four times. It is worthy of note that at times salyrgan therapy has to be continued for a long time before it becomes efficacious and it may well be that a certain degree of liver efficiency is necessary before a diuresis is possible. The case also illustrates the fact that acute liver failure may be superimposed upon a symptomless or nearly symptomless cirrhosis and, if properly handled, may not be inconsistent with almost complete recovery.

The patient has completely abstained from the use of alcohol and has been extremely careful in her manner of living and eating. As a result, her strength has gradually returned and one year after discharge from the hospital she is in apparently good health with no evidence of edema, ascites, or jaundice, although the liver and spleen are still easily palpable. A second case is of interest as illustrating how thorough a recovery can be made from what is apparently complete hepatic insufficiency when treated by adequate measures.

The patient was a woman, forty-seven years of age, with a negative past history except for a mild attack of catarrhal jaundice at the age of twenty.

Four months prior to admission to the hospital the patient was bothered by joint pains and was treated with fairly large doses of cinchophen (farastan). At about the time that cinchophen therapy was initiated the patient had a severe upper respiratory infection which lasted for several weeks. Two months before admission she noted the onset of malaise, weakness and nausea and a week later noted jaundice, dark urine and clay color stools. She stayed in bed for a few days but was up and around for six weeks before admission with increasing loss of strength, increasing jaundice and itching. For three weeks before admission there was edema of the feet and swelling of the abdomen. She had, in addition, a dry cough and a pleuritic pain at the left axilla which persisted for several weeks before admission.

Physical examination showed a deeply jaundiced, fairly well-developed and nourished woman with purpuric spots over her body and excoriations from continuous scratching. There were signs of a bilateral hydrothorax and, in addition, there was obvious ascites and edema of the legs and ankles. Careful palpation showed the edge of the liver to be about 3 fingers below the costal margin and tender. The tip of the spleen was just palpable. Laboratory examinations showed a highly colored urine containing a large amount of bile,

and light brown stools. The red count was 3,900,000, the white count 7000, hemoglobin 60 per cent, differential not remarkable. A bromsulphalein test showed 85 per cent retention of the dye at the end of one-half hour. A quantitative van den Bergh showed 5.5 mg. bilirubin per 100 cc. of blood.

Treatment was instituted promptly and consisted of absolute rest in bed, discontinuance of cinchophen, a diet containing about 450 Gm. of carbohydrate a day and the intravenous administration of 1000 cc. 10 per cent glucose in normal saline. The intravenous glucose was discontinued after four days because of the striking clinical improvement. A marked diuresis was obtained after the fourth day and a high urinary output was noted from this time throughout the following eighteen days. There was a corresponding loss of weight and improvement in the signs and symptoms. Within eight days there was an actual loss of 24 pounds with complete disappearance of ascites and edema. Jaundice also rapidly diminished and at the end of three weeks the quantitative van den Bergh was only 3.5 mg. per 100 cc. and a bromsulphalein test showed only 25 per cent dye retention at the end of an hour. At this time the liver and spleen were not palpable.

Such a rapid change in a very striking clinical picture illustrates well several facts. In the first place, the physical signs were those of almost complete liver insufficiency with jaundice, purpura and abnormal retention of water in the tissues and serous cavities. The patient was seen by several consultants and all agreed that her condition was precarious. The cause of the hepatic disturbance was obviously cinchophen, a known liver poison, and very grave concern was held regarding the prognosis. In spite of this, very simple treatment was associated with a very striking reversal of the picture, with all the signs and symptoms disappearing very rapidly. In this case the three important factors undoubtedly were rest, removal of the specific toxin, and an adequate carbohydrate intake. One point to be particularly noted was the very striking retention of fluid due to liver insufficiency with a rapid restoration of normal fluid balance once the liver cells had been restored to normal function. It is also of interest to note that the patient's recovery was complete and there had been no untoward symptoms during the past four years.

**Summary.**—The preceding protocols bring out practically all the essentials of successful treatment of hepatic insufficiency. The two patients were critically ill from what amounted to subacute yellow atrophy. The various functions of the liver were restored to normal by the measures already stressed, namely, rest, removal of toxin, adequate carbohydrate intake, the use of diuretics, and abdominal paracentesis when

required, blood transfusion, and iron therapy. Rarely the use of alkali to combat an existing acidosis due to failure of deaminization of amino acids is indicated, but in these two instances this was not the case. By similar measures it undoubtedly will be possible to successfully treat almost any type of liver disturbance, infectious or toxic in nature, provided surgical measures are not indicated. The essential considerations are a proper evaluation of the degree of liver insufficiency, the speed with which treatment is instituted, and the thoroughness and persistency with which the various measures are carried out.



## CLINIC OF DR. FREDERICK C. IRVING

BOSTON

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### PRENATAL CARE IN PRIVATE PRACTICE

I SHALL present for your consideration the case of Mrs. R., a primipara of twenty-two, who came to my office on January 15. Her last menstrual period began November 5 and there has been no bleeding since this date. She has always been regular in her catamenial habits since she first began to menstruate at the age of fourteen and she has never skipped a period. The flow has always been moderate in amount, appearing every twenty-eight days, and never requiring more than four pads on any one day. She never passes clots. The duration of the period is usually five days. There is no pain either just prior to the period or during its course, and there is no interference with her daily routine of life. She was married on September 5. Neither she nor her husband have taken any contraceptive precautions, as they have both wanted children.

It is apparent that Mrs. R. has had a normal menstrual history and the presumption is that she is pregnant. The next step is to ascertain if she has any of the other early subjective evidences of gestation. She says that about a month after missing her first period she began to have considerable nausea on awakening and that on several occasions she has vomited her breakfast. This condition still persists. When questioned regarding the condition of her breasts, she states that they are tender and distinctly enlarged. She has to urinate more frequently during the day and must arise for this purpose once during the night, which has never been the case before. She is sleepy at times and finds herself taking naps during the afternoon.

Before proceeding to a physical examination it will be convenient at this point to go into the patient's past history.



Both her parents are living and have had no serious illnesses. She is the oldest of three children. She had measles in childhood and has had her tonsils removed twice. An appendectomy without drainage was performed at fourteen. She has had no other surgical operations, nor has she broken any bones. She has never had scarlet fever, diphtheria, pneumonia, rheumatic fever or heart or kidney disease. Since the removal of her tonsils she has not been subject to sore throats or colds. Her weight has not varied much for the past two years. She plays ordinary games for pleasure but does not consider herself particularly athletic.

The patient is of medium height and weighs 120 pounds. General examination reveals nothing of interest. Her teeth are good. Examination shows the second laryngological attack upon her tonsils to have been victorious. The heart and lungs are normal. The breasts show no abnormalities, but the veins underlying the skin are prominent. The nipples project from the areolae, which contain a number of enlarged Montgomery's tubercles. The abdomen is negative, save for a linear scar about 2 inches long in the right lower quadrant. There are no herniae. The fundus of the uterus is not felt above the symphysis nor are any abdominal tumors made out.

The feet are placed in stirrups, the legs draped with a sheet. My nurse washes her hands and then prepares the vulva with cotton pledgets soaked in mild soap solution and warm water. I wash my hands and draw a dry sterile glove onto my left hand. Strict surgical asepsis is not necessary for such an examination. The labia are separated with the right hand: the mucous membrane of the introitus is slightly blue. The left forefinger, well covered with surgical lubricant, is gently introduced into the vagina, being particular to avoid the clitoris, which may be quite sensitive. I find by bimanual examination that the uterus is slightly enlarged and somewhat soft. The tissue about the external os is velvety in texture. Mrs. R., who is somewhat apprehensive, contracts her abdominal muscles so that further investigation is impeded, although she says that I have not hurt her. I therefore direct my nurse to raise the head of the table and I ask the patient to breathe deeply. These expedients have the desired effect. I am now able to introduce both my fore and middle fingers

and palpate bimanually each time the patient expires. I find that there is a distinct softening at the isthmus of the uterus, the so-called "Hegar's sign." I can feel the left ovary, which appears normal; the right I cannot make out. I reach cautiously for the promontory of the sacrum but am unable to touch it. The vaginal examination is completed by the introduction of a well-lubricated vaginal speculum. The portio vaginalis is distinctly purplish, the external os is nulliparous in form; the discharge is clear mucus and normal in amount and there are no cervical polyps visible.

With the patient in the same position I palpate and measure the pelvic outlet. The symphysis is of normal height and inclination; the arch is wide, being Roman rather than Gothic in architecture. I show Mrs. R. the outlet pelvimeter, and tell her that from now on I shall take measurements only, that there will be no further internal examination and that she will not be hurt. I insert my thumbs in the rings of the pelvimeter and place them upon the ischial tuberosities. The widest measurement so obtained is the correct one. I find it to be 10 centimeters, which is quite normal, and then measure Schuman's pubotuberous diameter, which is obtained by placing one tip of the large pelvimeter upon the left ischial tuberosity and the other upon the top of the pelvic bone. This distance is 10.5 cm., which is also normal. So far I have found that the pelvis is not male or funnel in type, since the outlet is not contracted nor is its height greater than one would expect in a normal woman.

The leaf at the foot of the table is raised and the patient's legs extended upon it. The legs are covered and the abdomen exposed. I place the tips of the pelvimeter upon the widest point of separation of the iliac crest and find it to be 28 cm. I then lay them upon the most prominent portions anteriorly of the iliac crests and make this measurement 25 cm. I ask Mrs. R. to lie on her left side and to bend the left knee, while she keeps her right leg straight. I identify the spine of the last lumbar vertebra and place one branch of the pelvimeter just below it while the other rests upon the anterior surface of the symphysis. I so obtain the external conjugate, which is 20 cm.

All of Mrs. R.'s measurements of the upper pelvis are nor-

mal. In general it may be said that whatever are the actual measurements, the interspinous is usually 3 cm. less than the intercrystal and the external conjugate 5 cm. less than the interspinous. When these proportions do not hold either there is gross pelvic deformity or, as is more frequently the case, the examiner is in error. The distance between the trochanters of the femora is not taken, because the measurement is of no value.

In spite of the information we have obtained regarding this patient's pelvis we have no real knowledge concerning the size of the interior, which is what interests us most, since the external measurements bear no close relationship to those within. However, since Mrs. R.'s long bones are normal for a woman of her height and weight, we may assume that her general skeletal development is also normal and that there is no reason to fear pelvic contraction. Accurate information concerning the interior of the pelvis can be obtained only by determining the diagonal conjugate, which, in Mrs. R.'s case, was impossible without anesthesia, or by x-ray measurements. x-Ray measurements are not indicated as a routine and are only of value at the end of pregnancy if the presenting part does not enter the pelvis.

I inform Mrs. R. that she is presumably pregnant. She wishes to know if more definite information can not be obtained by performing the "rabbit test," about which one of her friends has told her. The reply is that the lapse of time will give an equally accurate answer and at no expense. There seems to be a tendency at present to perform the Aschheim-Zondek test in cases where an immediate diagnosis is not essential. This probably results from a desire to employ so-called "methods of precision" and to avoid making a diagnosis on the basis of skill and personal experience. It should be remembered that the Aschheim-Zondek test and its modifications are not invariably accurate and that false negatives have on some occasions been reported in early pregnancy.

Mrs. R. is then instructed regarding prenatal care. She is directed to come to the office every month until the last three months of her pregnancy, after which she will be expected to report every two weeks. An appointment is made for her next visit and a card bearing the date and hour is

given to her for a memorandum. The nurse, who reports that the specimen voided in the office is normal, gives her a small clean bottle containing a few drops of chloroform as a preservative and enclosed in a mailing case. She is instructed to place in the bottle a mixed day and night specimen of urine, obtained by saving what she voids on going to bed, and what she passes during the night and on arising in the morning. She is also warned to place in the mailing tube a slip of paper bearing her name, since the identification of unmarked specimens is difficult, if not impossible. These specimens may be sent conveniently by mail. When they arrive at the office the color, reaction, and specific gravity are noted. The filtered urine is tested for albumin by the nitric acid method. If a suspicious ring is obtained the heat test is performed on a specimen. If albumin is found the centrifuged sediment is examined microscopically. The urine is always tested for sugar, since only in this way can the presence of latent diabetes be detected. If a reducing substance is found it may be glucose or lactose. Yeast ferments glucose but not lactose. A blood sugar determination is indicated when a positive sugar test is obtained.

It is well to follow a definite routine in instructing new patients so that nothing essential will be left out. The instructions apply to diet, care of the bowels, exercise, rest, clothing, bathing, and end with a brief recapitulation of the untoward events which should lead the patient to consult the doctor immediately.

Mrs. R. informs me that she has a considerable amount of nausea and that she occasionally vomits in the morning. She is told to eat two unsalted crackers and to drink a little water or a cup of black coffee before rising and to stay in bed half an hour thereafter. Her breakfast is to be a small one, consisting of cereal, dry toast and coffee; or a boiled egg, dry toast and coffee with orange juice. At 10:30 A. M. she has a slice of bread and butter and a glass of milk or a cup of cocoa. At 1.00 P. M. she has her luncheon, which may consist of soup or broth, a green vegetable or salad, bread, toast or rolls. At 4:30 P. M. she has tea. In addition there is toast, or bread and crackers with strained honey, jam or marmalade. At 7:00 P. M. she has a light dinner consisting of meat and vegetables

with soup or dessert. Before retiring Mrs. R. has a glass of milk or a cup of cocoa with bread or crackers. All fats, such as cream, or an excess of butter, or olive oil in salad dressing, are avoided; also fat meats, as bacon, ham, pork, certain fishes (salmon, herring, mackerel, bluefish). No food should be fried. On the other hand, carbohydrates may be given freely, including those containing sugar. Lean meat has no harmful or beneficial effect.

The patient is told to go about her daily activities with as little regard to her nausea as possible. She is asked to report by telephone if she does not improve within a week and is told that if she still feels ill a prescription will be sent her. This will consist of sodium luminal,  $\frac{3}{4}$  grain, to be taken twice or thrice daily.

Mrs. R. says that she has always been constipated and that this condition is even more marked since she has skipped her periods. The necessity of regular daily bowel movements is impressed on her. She is told that green vegetables, whole wheat bread, bran, cereals, 6 to 8 glasses of water daily and the habit of using the toilet at the same time every day will do much to set things right. If a laxative is needed it is administered preferably at night in pill or tablet form, as less likely to provoke nausea. Mineral oil, while excellent, is more appropriate later in pregnancy, when the stomach is in a more receptive condition.

Many dentists believe that the administration of calcium and vitamin D will prevent dental caries. Two glasses of milk, about 500 cc., contain 0.5 Gm. of calcium, which with the amount obtained in other foods should be enough for the needs of the fetus. If the patient does not like milk or if the physician fears that its ingestion will produce too marked a gain in weight, calcium may be provided in the form of gluconate or a similar absorbable form. Vitamin D may be given in any of the standard preparations.

The patient is told to forego all forms of athletic exercises, but to take a walk every day, lasting from half an hour to one hour. She is not to lift heavy objects or reach for things on high shelves or hooks which may require her standing on tiptoes. She may take warm baths, but is to avoid those which are very hot or cold. She is to mark off on a calendar

the days when she would be menstruating if she were not pregnant and is to avoid intercourse, undue exertion or social activities at those times. She is to take a rest every afternoon and to be in bed by 10 o'clock except when she goes out in the evening for entertainment, which should not be more than twice a week.

Her clothing should be appropriate to the season. Constriction of the waist is avoided and clothes are to be hung from the shoulders. Round garters or rolling the tops of the stockings may predispose to varicose veins. Shoes should be comfortable with moderately low flat rubber heels. If she habitually wears a girdle she may continue to use it until it becomes too tight. Later a maternity support may be required, but this depends solely upon the patient's comfort and confers no particular benefit upon the mother or child. Should it be necessary to order such a support the patient is sent to a corsetiere who will carry out the doctor's wishes. Many dealers in such garments, if not checked, will sell the patient an elaborate and expensive corset which is only of use to very large, stout women.

Mrs. R. is told that she is to report by telephone immediately and go directly to bed if she has any vaginal bleeding or abdominal pain. She is also informed that she is to consult me freely if anything occurs which she does not understand or if she wishes any advice. She is cautioned against the medical lore of her married relatives and friends. At this time also she is warned of the other danger signals of later pregnancy which are indicative of toxemia such as headaches, blurring of vision, abdominal pain and swelling of the face or extremities.

Over half an hour has been spent at the first call. Subsequent visits will require less time, as it will only be necessary to take the patient's blood pressure, weigh her and ask her certain routine questions. In early pregnancy these concern bleeding, abdominal pain, the frequency with which her bowels move, and the general state of her health. At the beginning of the second half of pregnancy one should ascertain the date of quickening and from this information calculate expected date of confinement to see if it agrees with that obtained by counting from the first day of the last period. In the event

of a marked discrepancy between the two dates, more reliance should be placed upon calculation from the last menstruation, since the first detection of fetal motions is entirely subjective and introduces an element of individual variation.

If all is going well it is not only unnecessary but an annoyance to examine the patient every time she comes to the office. Any symptoms, however, should be carefully investigated. About two months before term the abdomen should be palpated to detect a possible breech presentation, since an external version may be more easily accomplished at this time than later in pregnancy. Three or four weeks before the expected date of confinement the patient is examined vaginally under strict aseptic precautions. The presenting part is identified and its station in the pelvis determined; whether it is low, mid, high or floating. One notes whether the portio vaginalis is shortened or effaced, the consistency of the cervix and how many fingertips the external os and the internal os admit. The diagnosis of position is made almost entirely by abdominal palpation. The fetal heart tones are ausculted. About this time the patient may ask if the baby is going to be a boy or a girl. The truthful physician will tell her that he does not know. If he ventures into the realm of prophecy he will be wrong half the time. A large uterus with confusing fetal landmarks, even though only one fetal heart is heard, warrants an x-ray examination to settle the question of twins. It may startle the patient and her husband as well as embarrass the doctor at the time of delivery if nature's generosity is not known beforehand.

Nothing more is heard from Mrs. R. until two weeks later, when she telephones to say that she has noticed the escape of a small amount of bright blood from the vagina, in all, less than a teaspoonful. There is no pain and she is now in bed. I tell her not to get up and that I shall see her as soon as possible. I also inform her that I shall want her to remain in bed for some time and that I shall send a nurse to her house to care for her. Since the original pelvic examination revealed no masses or abnormal tenderness it is unlikely that the bleeding indicates an ectopic pregnancy; rather are the chances in favor of a threatened abortion.

I find the patient in bed and perfectly comfortable. There

is a little fresh staining on the vulvar pad. I do not make a vaginal examination for fear of loosening further the ovum from its attachment. I cautiously palpate the lower abdomen. I feel the fundus of the uterus just at the symphysis pubis, which is commensurate with the estimated duration of pregnancy. There is no tenderness anywhere. She says she still feels slightly nauseated but that things have improved greatly. I instruct the nurse to keep Mrs. R. in bed. She is to use the bed pan instead of the toilet. She may have two pillows but is not to sit up. No attempt is made to move her bowels for twenty-four hours, when she is to have an oil enema, to be followed later by mineral oil by mouth. Most authors of textbooks advise the use of morphine in threatened miscarriage to diminish uterine irritability, but this therapy seems to be based on a misconception of the mechanism of miscarriage. The first step in abortion is bleeding into the spongy layer of the decidua basalis. It is not until the hemorrhage becomes of sufficient extent to distend the uterus or separate the ovum that the uterus reacts and attempts to expel the product of conception. It is therefore difficult to see what beneficial effect morphine can have in preventing the completion of an abortion, although its use is justified to relieve pain when an abortion is actually in process. The application of an ice-bag to the suprapubic region can do nothing unless it is to stimulate uterine contractions, which is what we wish most to avoid.

Mrs. R. remains in bed for one week after all bleeding has stopped. The first day up she is allowed to sit in a chair; the next day, although restricted to the same floor, she may walk about and the third day she may go downstairs to dinner. Her activities are gradually expanded and the nurse is omitted. On wholly empirical grounds the patient is given a half a grain of thyroid extract daily and is encouraged to eat articles containing vitamin E, such as lettuce, corn, and wheat germ. If the attendant wishes he may attempt to increase the amount of progesterin (corpus luteum hormone) by administering a suitable glandular product, if he realizes that there is at present no convincing clinical experience to justify him in his course of treatment. Intercourse, exertion, travel and auto-mobiling are forbidden for at least a month.

For the present Mrs. R.'s pregnancy progresses normally.



At her visit of April 9 I find that she first felt the baby move on March 24. Since she is a primipara I add twenty weeks to this date and find the expected date of confinement to be August 11, which agrees well with the date of August 12 obtained by calculation from the first day of the last period. She feels very well indeed and is evincing interest in food.

On May 7 I find that Mrs. R. has gained 5 pounds since her last visit. Her urinalysis and blood pressure readings are normal. The question of diet is discussed in some detail. She has been to visit her mother, who has urged her to eat large quantities of food so that she may have a nice, large, healthy baby. Patient explanation at least partially convinces Mrs. R. that the amount of food she eats will have very little effect on the size of the baby, but will have a very considerable effect on her. She is told that an accumulation of fat will make it more difficult for her to give birth to the baby and that it may make the difference between a normal and an operative delivery. The final argument that a great increase in weight may spoil her figure appears to produce some impression. She is told to weigh herself twice a week on the same scales and not to gain more than half a pound a week. A printed diet list is given her, showing the caloric value of various foods and she is instructed to restrict her daily intake to 2000 calories. She is especially cautioned against an excess of fats, sweets and starches.

At Mrs. R.'s next visit on May 21, I find that she has attended faithfully to her diet and has only gained 1½ pounds in two weeks. She complains of constipation and heartburn. She is told to eat plenty of fruit, green vegetables and whole wheat bread. A suitable preparation of bran is advised for breakfast. She is instructed to cultivate regular hygienic habits and to drink an adequate amount of water, 6 to 8 glasses daily. A tablespoonful of mineral oil is prescribed half an hour before each meal and at bedtime, with instruction if the oil should escape by rectum to reduce each dose, but not the total number of doses. For the heartburn calcium carbonate is prescribed in 5 grain tablets to be carried with her and taken *ad libitum*. She is also cautioned to avoid spiced, fried or highly seasoned foods and is warned that no per-

manent improvement may be expected until after the birth of the baby.

On July 16 Mrs. R. has her antepartum examination. The portio vaginalis is shortened but not completely obliterated; the external os admits a fingertip, but the internal os is closed. The lowest part of the vertex is just above the imaginary line joining the ischial spine. Abdominal palpation also shows the head to be engaged, the fetal small parts are felt in the right flank and the fetal heart is best heard on the left. The position is left occiput anterior. The uterine fundus is almost at the costal margin.

On July 30 I find that Mrs. R. has gained 6 pounds in the last two weeks. Her ankles are slightly puffy and her face is beginning to have the full appearance characteristic of edema. The blood pressure is 120/84 and the urinalysis is negative. However, the sudden increase in weight is suggestive of an approaching toxemia. She is told to take a tablespoonful of Epsom salts in water after returning home and to take the same dose morning and evening of the next day. Meat, fish, eggs and salt are eliminated from her diet and her fluids are restricted to 4 glasses of water daily. She is told to return in two days and to telephone at once if she has any headaches, blurring of vision, double vision, specks before the eyes, abdominal pain or increase in the swelling of her face, hands or feet.

She returns in two days and looks slightly improved. There is less facial and dependent edema and she has lost 3 pounds. The blood pressure has risen to 150/96. The urine is more concentrated, but it still contains no albumin. However, the hypertension is sufficient to alarm me and I tell Mrs. R. that I want her to enter the hospital that day so that we may treat her more thoroughly and observe her constantly. She wants to know if it will not be satisfactory to carry out the same policy at home. She is informed that this cannot be done and that her interests and those of the baby demand the best possible care. She says that she must confer with her husband and will let me know her plans later in the day.

After she has left the office I call her husband on the telephone and discuss the situation. I describe to him briefly the nature of eclampsia and tell him that it is practically a

preventable disease but that I must have his and Mrs. R.'s cooperation if I am to take the responsibility. He informs me that I may count on them both and she enters the hospital that evening.

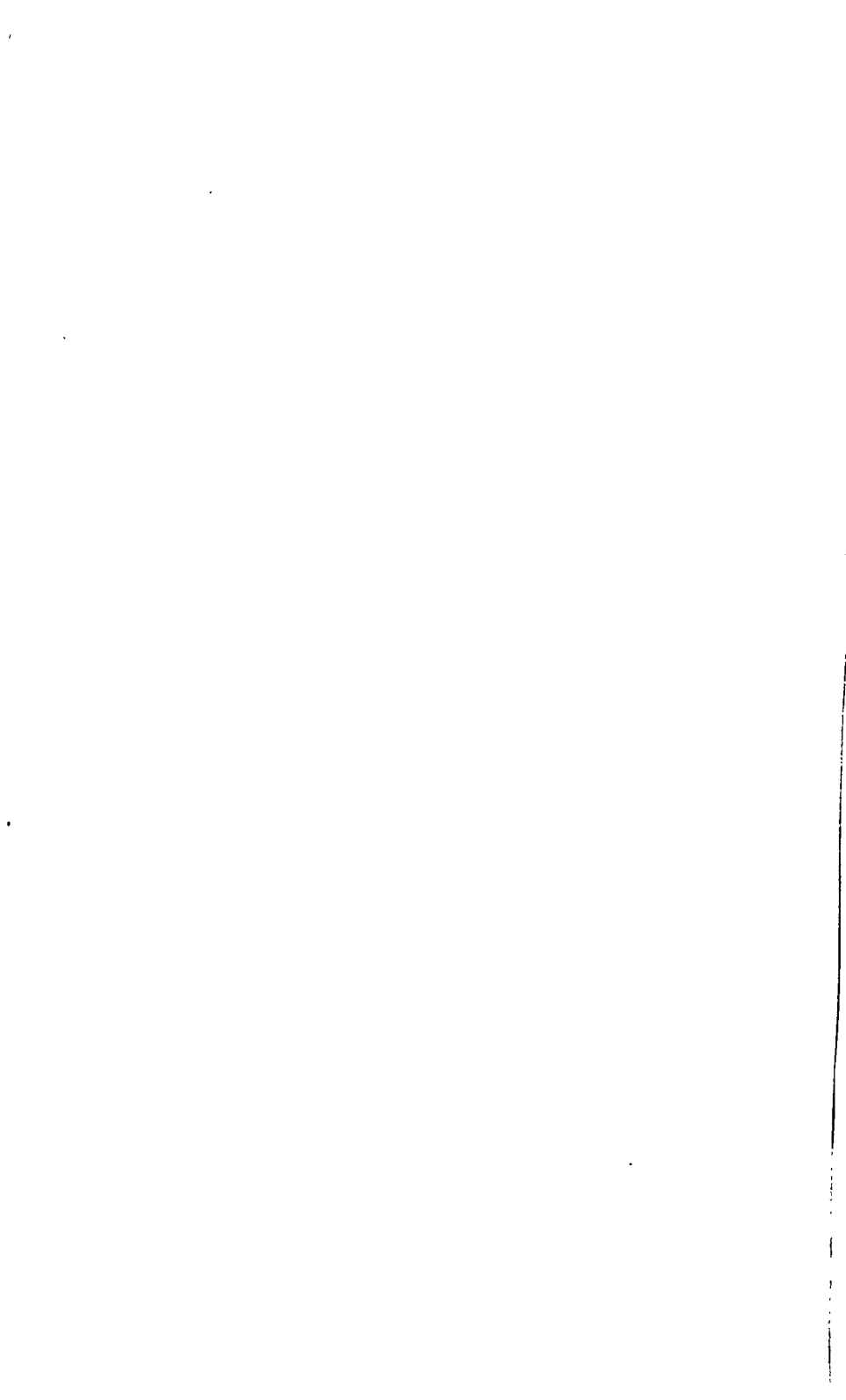
When the patient is admitted she is put to bed and is not allowed up until it is so ordered. A catheter specimen of urine is obtained for examination and a blood sample for the determination of the nonprotein nitrogen, urea nitrogen and the uric acid. The first day she is given nothing by mouth but 600 cc. of water. The next day a milk diet is begun to the extent of 800 calories, which is gradually increased up to 1600 calories. The fluid output, including liquid feces, is measured. In no event is the fluid intake allowed to exceed the output. Immediately on entrance 1 ounce of a 50 per cent or saturated solution of magnesium sulphate is given by mouth and is repeated every hour unless the patient is asleep. This is continued until there are from 12 to 13 watery stools a day after which the frequency of the dosage is reduced. Few women whose bowels are moving freely develop eclampsia.

The limitation of fluids and the vigorous catharsis produces a marked reduction in the edema so that Mrs. R. loses 8 pounds more. Her face is less puffy and the pitting edema over her ankles has largely disappeared. The blood examination shows: N. P. N. 30.00, B. U. N. 14.00, U. A. 4.00, which is not remarkable. The blood pressure falls the day after admission to 130/90 and remains in that general vicinity. There are no headaches, visual disturbances or epigastric pain. The urine, which becomes quite concentrated, shows a trace of albumin and the sediment reveals hyaline and granular casts with occasional red blood corpuscles. The amount of albumin varies from day to day, but is never less than a slight trace.

It is evident that Mrs. R.'s condition has improved since entering the hospital but that she has not completely recovered, nor is she sufficiently improved to permit her return home. There seems to be no immediate danger of convulsions, but since preeclampsia is followed in a considerable number of cases by permanent vascular hypertension we must consider the advisability of terminating pregnancy. The child is practically mature, being within the last two weeks of pregnancy and there is no cephalopelvic disproportion. Exam-

ination shows the portio vaginalis to be effaced and the os one fingertip dilated. Accordingly, Mrs. R. is given 2 ounces of castor oil early in the morning and an enema two hours later. Her membranes are then ruptured artificially under strict aseptic precautions. Within an hour uterine contractions have begun and the delivery of a normal infant weighing  $6\frac{1}{2}$  pounds occurs in the evening.

Mrs. R.'s subsequent course is uneventful. Her blood pressure falls after delivery to 120/74. A catheter specimen of urine a week postpartum contains only the slightest possible trace of albumin and the sediment is negative. A similar specimen on discharge from the hospital contains no albumin. When she was seen six weeks and six months after delivery her condition was normal in every way.



CLINIC OF DRS. WILLIAM E. LADD  
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CHILDREN'S HOSPITAL

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IDIOPATHIC ULCERATIVE COLITIS IN CHILDREN

**Definition.**—Idiopathic ulcerative colitis is a disease not only difficult to treat but difficult even to define adequately. The patients whom we would include under this title are those who suffer from a chronic bloody mucous diarrhea, and who show ulcerative lesions in the colon for which no etiologic factor can be found. The disease may be mild or severe. It occurs most commonly in early adult life but is not infrequently found in the first twelve years of life, and it is with this age group that this paper is concerned.

**Etiology.**—In our opinion the etiology of the disease is still unsettled. Numerous theories have been advanced to explain it. The disease is generally believed to be of infectious origin. Numerous bacteria have at one time or another been considered to cause the disease. Bargaen has presented a good review of the literature, and the possible bacterial etiology of chronic ulcerative colitis, and described a diplococcus known by his name as the causative organism. We do not feel that the evidence is sufficient to accept the Bargaen diplococcus as the cause of the disease.

Twenty-three of the patients of our series have had a detailed bacteriologic study. Cultures were taken from stools and also in many instances directly from ulcerations at the time of proctoscopic examination. The study of these cultures has not shown the consistent presence of any one organism to which pathogenic significance could be attached.

The Bargaen diplococcus was isolated in 8 instances and a late lactose fermenting organism, similar in its other cultural characteristics to the paratyphoid group, was isolated

from 2 patients. In 1 patient cultures taken directly from the ulcers showed a hemolytic streptococcus and a *Bargen diplococcus*.

**Pathology.**—The ulcerative process of the colon in this disease is of characteristic appearance though subject to variation in amount and extent of distribution. It commonly involves the rectosigmoid segment and descending colon but may be extended to the whole colon and an occasional case has been reported in which the lower portion of the ileum was also involved. The ulcerations are typically small and placed close together leaving very little mucous membrane unaffected, and giving in the gross a red granular appearance rather than widely separated individual ulcers. As the disease progresses the ulcerations extend to the deeper layers of the colon, replacing the muscle layers with scar tissue or eventually, at times, penetrating all layers and resulting in perforation and localized abscesses or peritonitis. The remote systemic findings consist in general emaciation, loss of weight, and in cases of long standing, a secondary anemia which may be of considerable severity. One or two of our patients have presented bizarre skin lesions and joint changes.

**Symptoms.**—The onset of the disease in children is usually insidious, although occasional cases may have an abrupt onset. Usually the first symptom noted is a gradually increasing frequency of bowel movements. These are often accompanied by cramps and abdominal discomfort. As time goes on the bowel movements become more frequent and mucus, often in considerable amounts, appears in the stools. Later, when numerous ulcers have appeared, the stools contain considerable pus and blood in addition to mucus. The number of watery bowel movements containing these abnormal elements usually varies from five to fifteen daily, although in some patients they may be much more numerous. Many such patients run a low grade fever although some may have normal temperatures. Because of the almost continuous loss of blood in the stools, the symptoms and blood changes of a moderately severe anemia are found.

The symptoms may continue unabated or with periodic remissions, for months or even years, during which time marked structural changes are occurring in the colon. Such patients

lead a very depressing and miserable existence. The more severe cases may be confined to bed. The less severe cases, while not bedridden, become social outcasts. They are unable to attend school or engage in the usual play of their associates because of the embarrassing frequency of bowel movements.

As the disease continues the nutritional state of the patient becomes increasingly poor. A great deal of weight is lost and marked retardation in growth and development occurs. There is usually fairly good compensation for the disturbances in water and electrolyte metabolism. This is probably because of the chronicity of the disease.

**Physical Examination.**—On general physical examination of these patients with idiopathic ulcerative colitis one does not find any definite characteristic except the general emaciation due to the wasting process and the pallor due to the secondary anemia. Occasionally on abdominal examination tenderness is elicited by pressure along the course of the colon. Proctoscopic examination in contrast to the general examination is quite characteristic. When the proctoscope is introduced one will see first a considerable amount of grayish, mucopurulent material. When this is washed or gently wiped away the mucous membrane appears red and granular with minute ulcerations diffusely scattered over its surface. The mucous membrane bleeds easily on very slight trauma. Perhaps the most striking characteristic of the proctoscopic examination is the fact that one sees almost no normal-appearing mucous membrane in contrast to other types of ulcerative colitis.

**Laboratory.**—*x*-Ray examination of a barium enema shows a characteristic change from the normal as soon as structural change has taken place in the colon. Early in the disease the haustral markings become shallow and infrequent, and later in the disease are entirely absent, giving what is usually described as a pipelike appearance. The bacteriologic findings in the stools will be considered as a part of the differential diagnosis.

**Diagnosis.**—The diagnosis of idiopathic ulcerative colitis is suspected in any patient with a history of chronic bloody mucous diarrhea who presents a characteristic picture on proc-



toscopic and x-ray examinations and after other conditions have been eliminated by suitable bacteriologic studies.

There are several conditions which have to be considered in the differential diagnosis. In children the most important conditions to be considered are amebic dysentery, tuberculous enteritis, chronic bacillary dysentery, and rarely Meckel's diverticulum. The acute diarrheas such as those caused by the dysentery bacillus and certain members of the paratyphoid group of organisms are seldom confused with chronic ulcerative colitis because of their acute onset and relatively short duration. Diarrhea associated with certain deficiency diseases such as pellagra, beriberi, or sprue should be considered through taking a detailed dietary history and seeking other clinical evidences of these disturbances. Malignant disease, diverticulitis, and polyposis are rarely seen in children and therefore do not as frequently offer a problem in differential diagnosis as in adults. Since the etiology and pathogenesis of chronic ulcerative colitis is not clearly understood, it is very important to exclude the above conditions before arriving at its diagnosis. In part, the diagnosis is arrived at by a process of elimination.

Amebic dysentery can be ruled out only by the careful examination of a considerable number of stool specimens by someone familiar with the appearance of both the cysts and vegetative forms of *entameba histolytica*. It should be emphasized that to be of value, stool examinations for ameba should be done as quickly as possible after the stool is passed. Furthermore, at the time of proctoscopic examination of a patient suspected of ulcerative colitis, material should be taken directly from the ulcers and examined immediately for amebae. In occasional cases with a suggestive history, such as residence in the tropics, but with repeatedly negative stool examinations for amebae, it may be worth while to treat the patient with some emetine preparation as a therapeutic trial.

The tuberculin test is of great value in the differential diagnosis of tuberculous enteritis *in children*. If this test is negative to the larger doses of tuberculin (*i. e.*, an intracutaneous injection of 1 mg.) it is reasonably certain that the enteritis is not of tuberculous origin. However, if the reaction is positive, a detailed and careful study is necessary.

Tuberculous enteritis usually involves the upper end of the large bowel or terminal ileum, and may be demonstrated by x-ray examination. Direct smears of fecal material, concentrated by antiformin, should be examined, and with negative results, such material should be injected into one or more guinea-pigs.

A true chronic bacillary dysentery is extremely rare in children, at least in our experience. It is ruled out by the repeated culturing of fresh fecal material. It should be emphasized that a number of stool cultures are necessary. A single negative culture is of no value whatever. Agglutination reactions with the patient's serum and a large number of stock antigens are of value. A large group of antigens should be used because there are so many serologically different strains of dysentery bacilli. In our own agglutination studies we use, in addition to the dysentery antigens, a number of different strains of organisms belonging to the paratyphoid group.

The symptoms presented by patients with a Meckel's diverticulum may, in an occasional instance, be confused with those in early cases of chronic ulcerative colitis. In the former disease bleeding into the bowel is not uncommon and occasionally diarrhea may be present. In such patients, changes in the colon are not demonstrable by x-ray following a barium enema and ulcers are not visualized at proctoscopic examination.

When a patient is admitted to this clinic with a history suggesting chronic ulcerative colitis the plan of diagnostic study carried out is as follows: the patient is kept at complete rest in bed and is given a low residue diet. The usual routine examinations such as complete physical, blood, and urinalysis are done. If the patient is febrile, one or more blood cultures are taken. Blood is also taken for a Wassermann reaction and for serum for agglutination with these antigens; *B. dysentery* Shiga, *B. dysentery* Flexner, *B. dysentery* Hiss-Russell, *B. dysentery* Sonne, *B. paratyphosus* A, *B. paratyphosus* B, *B. enteritidis*, and *B. abortus*.

Several freshly passed stool specimens (4 or more) are examined for the presence of *entameba histolytica* and for the cysts of this parasite as well as being cultured for pathogenic organisms.

Intracutaneous tuberculin tests are done starting with 0.01 mg. of tuberculin. If the reactions are negative to the smaller doses, the dosage is increased to 1 mg. of tuberculin. If the tuberculin reaction is positive a thorough search is made by roentgen ray for any parenteral focus of infection. Stool specimens are carefully examined for tubercle bacilli by the methods described above.

The colon is examined by roentgen ray following a barium enema in order to appraise the amount, location, and characteristics of any structural change that may be present.

The child is finally subjected to proctoscopic examination (under anesthesia) in order to visualize any ulcers that may be present. At this time material is swabbed directly from the ulcers for smear examination, ameba search, and cultures.

The diagnosis of idiopathic chronic ulcerative colitis is arrived at only after all the data from such a study has been collected.

**Treatment.**—After a diagnosis of idiopathic ulcerative colitis has been reached the question of what form of treatment should be employed naturally arises. On this subject there is little uniformity of opinion at the present time either as regards the general principles or the details. This situation has arisen for two reasons, one that there is a wide variation in the severity of the disease and, two, that in the more severe types of the disease no form of treatment is uniformly successful or curative. Broadly speaking, medical treatment is employed for a limited period of time for those patients in whom the diagnosis is doubtful or in whom the disease is mild and has been present for a short time only. The medical treatment consists of rest and general good hygiene. The patient is placed on a low residue diet containing an adequate amount of the essential vitamins. If the secondary anemia is marked it is combated by a soluble form of iron and transfusions. The use of opiates to control diarrhea is of doubtful wisdom on account of the chronicity of the condition. Such drugs as bismuth subnitrate or subcarbonate have been found to be of little value in our experience. Colonic irrigations are not of value, are painful, and must be dangerous on account of the possibility of causing perforation if the disease is of long duration. Autogenous vaccines made either from cultures of

the Bargaen diplococcus or other organisms isolated from the feces of these patients have been of no therapeutic value in our experience. The use of a serum would seem somewhat illogical until such time as the causative organism has been proved beyond peradventure.

The question of the indications for surgical treatment and what form of operation should be done is again one that lacks uniformity of opinion. It is our belief that the unpleasantness of the operation has in most instances caused an unwarranted delay in its adoption. This delay has removed any possibility of curing the disease. We believe that the almost universal prolonged persistence of medical treatment of one form or another accounts for part of the usual pessimistic surgical point of view. There are two logical reasons for resorting to surgical treatment. The first is to save the life of a patient who is going downhill rapidly during the course of the disease. The second is to limit the progress of the disease and improve the patient's general condition, removing him from a state of chronic invalidism. The operation which we advocate for fulfilling these reasons is transverse ileostomy with complete external diversion of the fecal stream. We have had no experience with appendicostomy, cecostomy, or colostomy, but feel that there is not sufficient evidence of their merit in the literature to warrant their employment. It cannot be claimed that ileostomy is a pleasant operation or that it can be performed without risk. It can be claimed, however, that it is at times a life-saving procedure and that the inconvenience and drawbacks of an ileostomy are less than those of the disease.

There have been 26 patients treated at the Children's Hospital on whom a diagnosis of chronic ulcerative colitis has been made. Of these 26 patients 10 have received medical treatment only. Three of these 10 in whom the symptoms were rather mild and of short duration, have apparently recovered and stayed well for variable periods of time. Whether they will later have remissions is a matter of surmise. The other seven still have the disease and have not been improved by the various forms of treatment used, including autogenous vaccine therapy. The remaining 16 patients have all had medical treatment without improvement for periods of several

months to several years before resorting to surgical treatment. There are two exceptions to this statement in the cases of two infants who will be referred to presently.

Though the results of the surgical treatment in this series are far from gratifying, still there are features in the series which are hopeful and which lead to the belief that the results may be improved.

All of these 16 patients have had an ileostomy performed. Four who had had the disease from five to two years before operation, had the ileostomy closed, in one instance eight years later and in the other three about two years after ileostomy. These 4 patients have been followed afterwards for four years and eleven months, three years and nine months, two years, and one year and two months respectively. They were all having normal stools, were in good general condition and so far as we could gather, were, for the time being, well. Whether they will eventually have remissions is, of course, impossible to say. Perhaps of more significance than these 4 cases is the history and unfortunate end-result in a boy who had an ileostomy performed when he was nine years and ten months old. This boy had a history of bloody mucous diarrhea for over seven years, not as severe as in some of the other patients, but increasing in severity during the six months prior to the ileostomy. He had 6 to 8 stools daily with blood and mucus, and he was losing weight. The proctoscopic examination revealed the characteristic ulcerations, and barium enemas given at six-month intervals showed increasing structural change of the colon. Subsequent to the ileostomy he improved rapidly, gained 17 pounds in weight in the first six months, went to school, indulged in active exercise, and in short, lived a very normal life. At the end of two years, closure of the ileostomy was being considered when he developed a volvulus of the jejunum with acute intestinal obstruction from which he died. The notes of the postmortem examination of the colon are of interest. Gross examination, "The mucosa of the colon appears to be practically normal except for a very fine roughening of its surface. It is not injected and there are no areas of ulceration. Hanging from the serosa of the colon are a number of small appendices epiploicae." Microscopic examination of the colon. "There is a single layer of

columnar epithelium over practically the entire surface of the colon. The mucosal surface is remarkably smooth. The glands are rather small, but their epithelium is remarkably well preserved. The tunica propria is infiltrated with a moderate number of large and small mononuclear cells and a few polymorphonuclear leukocytes. There is slight congestion here also. The solitary follicles are markedly depleted of lymphocytes and infiltrated moderately by large mononuclear cells. There are fairly numerous small areas of necrosis just under the intact epithelial surface. One healed ulcer now covered by epithelium is noted." The pathologist, Dr. Farber, comments, "The findings here are of great importance in reference to the efficiency of the rest treatment of the colon by surgical means. Certainly there was no evidence of an active ulcerative colitis at the time of autopsy."

Besides the 4 patients who had the ileostomy closed and were at the last report apparently well, there are 5 patients in this series who have the ileostomy still open. One boy who had had the disease since he was ten years old, had an ileostomy at fourteen years of age. He was very emaciated, weak, confined to bed, and in very poor general condition. Following the ileostomy his condition improved markedly. He gained weight, was able to be up and lead a fairly normal life. Three years later proctoscopic examination revealed an active process in the colon. This patient may be a candidate for colectomy. He is not a candidate for closure of the ileostomy. Another patient who had had the disease only eight months when the ileostomy was performed, had a rather stormy course for a few weeks following operation, but at last note, eighteen months later, was in excellent condition. This patient may be able to have the ileostomy closed later. A third patient, a girl, contracted the disease at the age of eight, and the ileostomy was performed four years later, when she was in very poor condition. During her convalescence she developed a very extensive ischio-rectal abscess. Examination two years later showed the patient in excellent general condition. We believe the ileostomy in this instance was a life-saving procedure, even though the disease is still present. Proctoscopic examination at this time revealed some mucopurulent discharge, a mucous membrane that bled on very slight trauma,

one small polyp, and an anal sphincter of doubtful competence. We believe this girl should have a colectomy. Two other patients in this series acquired the disease in the first year of life. Prior to the appearance of the disease in these two infants we were not aware that it ever occurred at such an early age. In both instances a very careful study was made to see if there were not some other etiologic factor and in neither case was any found. Both infants had very careful medical care and ileostomy was resorted to only when a fatal outcome seemed imminent. In both instances great difficulty was experienced in maintaining adequate body fluids, both before and after ileostomy. The continuous introduction of saline solution intravenously proved to be very helpful and was continued for more than a week in both patients. The older of the two, who was seven months when the ileostomy was performed, was in good condition at the age of two years except for a slight rectal stricture which dilated readily. We believe this ileostomy can be closed soon. The younger of the two infants has had the ileostomy for seven months and is in good health at the present time. It is still too early to hazard a guess about the closure of the artificial opening.

There have been 7 deaths in this series of 26 cases, some directly attributable to the disease or its treatment and some of doubtful connection. One case has already been mentioned, the boy who did well for two years and then acquired a volvulus of the jejunum and died of intestinal obstruction. Another boy of thirteen who had the ileostomy performed in the seventh year of the disease, did exceptionally well for six months afterward. He had gained 40 pounds in weight when he developed carcinoma of the transverse colon, from which he died. A girl of nine years died of multiple perforations of the colon and peritonitis a week after she had the ileostomy performed. A boy nine years old who had had the disease over three years, died of perforation one month after ileostomy had been done, and another who had been followed medically at the Children's Hospital, died a few days after an ileostomy had been performed in another hospital. One patient who had done well for two years after the ileostomy, had a streptococcus infection of the wound following the operation for closure, and died, it was believed, of a streptococcus peritonitis. The

seventh patient died following an ileostomy and was found to have an ileitis as well as chronic ulcerative colitis at the postmortem examination.

**Impressions.**—It is doubtful whether conclusions are justified from so small a series of cases, but we have several definite impressions.

1. The cause of the disease is still unknown.
2. Diagnosis of idiopathic or chronic ulcerative colitis without careful bacteriologic, x-ray, and proctoscopic examinations is not warranted.
3. The disease has varying degrees of severity.
4. We regard the idea expressed by McKittrick and Miller that ileostomy should be considered a permanent condition, as slightly too pessimistic to apply to our age group.
5. Ileostomy is at times a life-saving procedure and is followed by rapid and lasting improvement in symptoms.
6. We believe ileostomy should be performed before too much structural change has taken place, if we are to avoid the artificial opening being permanent.

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## CLINIC OF DR. CLARK W. HEATH

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### THE CLINICAL SIGNIFICANCE OF PROBLEMS OF AB- SORPTION IN THE HUMAN GASTRO-INTESTINAL TRACT

It is becoming increasingly evident that diseases due to nutritional deficiency may occur even when the diet seems to be adequate. Materials valuable to the body may be lost, for example, by hemorrhage from any part of the body, or by loss through the kidneys owing to disease of these organs. During growth, pregnancy, and in other conditions such as fever or hyperthyroidism, in which increased demands are made upon the body stores for necessary materials, dietary deficiency disease may result if the increased demands are not met by an adequate supply of substance derived from the food. In such conditions as sepsis, cancer and dysfunction of certain organs, necessary material, though present in the body, may not be properly utilized. The diet, moreover, may be quite adequate for a normal person, but because of an insufficient secretory mechanism in the gastro-intestinal tract, substances may not be made available for the body. Castle has demonstrated how such a mechanism may be productive of Addisonian pernicious anemia. In this disease there is a deficiency of an enzyme-like substance in the gastric juice, the presence of which, in normal individuals, produces by the interaction with certain materials of the food a specific substance necessary for normal blood formation. Lastly, the diet may be adequate, but because of various gastro-intestinal abnormalities with or without diarrhea, food substances may not be absorbed and therefore not reach the body itself. Minot, Strauss and

Cobb<sup>1</sup> have summarized the trend of knowledge regarding these factors in deficiency disease as follows: "One must also recognize that dietary deficiencies can develop because of disorders of the gastro-intestinal tract. Necessary material may not be properly elaborated because of a lack of gastro-intestinal secretions, as occurs in pernicious anemia, or nutritious elements may be absorbed unsatisfactorily, leading to a state of deficiency exactly as if an insufficient amount of proper food had been ingested."

The study of the normal mechanism of intestinal absorption has been pursued intensively by physiologists for many years. Physicians, moreover, have been aware for a long time of the importance of absorption in various aspects of medicine, for example, in the principle of the administration of cathartics, or in the choice of giving medicinal substances parenterally rather than orally. The presence of good teeth for mastication, and adequate preparation of the food by cooking have been long recognized as important factors for the assimilation of food. It is only recently, however, that the influence of absorption upon the causation of disease has attracted interest. It is timely, therefore, to summarize our conceptions of the pathologic physiology of absorption, to indicate the position it takes in clinical medicine, and to outline methods of clinical study and of treatment.

**The Mechanism of Intestinal Absorption.**—"Absorption" refers to the transfer of substances across the membrane of the intestine, so that they are made available to the body as a whole. Ingested substances are, for all practical purposes, still outside the body until they have passed the intestinal barrier. The preparation of food substances for absorption by the action of the various secretions of the digestive organs is, of course, intimately linked with the process of absorption itself. It is therefore obvious that impairment of the gastro-intestinal secretory mechanism and the absorptive mechanism may be difficult to separate clinically, and it is reasonable not to attempt to differentiate them too dogmatically.

In order to approach the problem of intestinal absorption in its relation to disease it is necessary to consider the normal mechanism of absorption. There seem to be innumerable fac-

tors which have to do with the absorption of substances in the intestine. *The nature of the substance itself* is of importance: its concentration and mass, state of dispersion, hydrogen-ion concentration, lipoid solubility, surface tension, and then also such factors as the nature of accompanying substances and of the external secretions of the gastro-intestinal tract. *The character of the bowel wall* is to be considered: the surface area (to which the number of villi contribute), the mechanisms of segmentation and peristaltic movement, the intra-intestinal pressure, the movements of the villi, the permeability of the intestinal wall, the blood flow in the capillaries, the so-called "vital" selective ability of the lining cells. The subject has been reviewed in detail by Goldschmidt<sup>2</sup> and Magee,<sup>3</sup> and one draws the general conclusion from their work that, although physicochemical laws, in particular those of osmosis, can explain only a part of the phenomena of absorption, the apparently selective ability of epithelial cells may eventually be explained as physicochemical knowledge progresses. The factors governing normal absorption in the intestine being so numerous, it can readily be seen how complex may be the physicochemical states which modify absorption when the intestine is altered pathologically.

Certain substances are absorbed more easily than others from the intestine. Iron and the materials potent in pernicious anemia and pellagra are substances which apparently are not absorbed with ease, as is suggested by the great discrepancy between effective dosage when these substances are given by the parenteral route as opposed to the oral route. It seems possible that vitamins are likewise absorbed with relative difficulty and that this may explain the development of syndromes associated with deficiencies of these substances when the intestinal mechanism is disturbed although the diet is complete.

**Clinical Evidence of Malabsorption as a Cause of Disease.**—Whereas there is abundant clinical evidence of disease which seems to be directly or indirectly the result of malabsorption, the concept is only with great difficulty amenable to scientific proof. One must first of all be assured that the dietary intake has been adequate. This evidence is frequently lacking, or is very difficult to obtain. Since disorders of the gastro-intestinal tract are accompanied almost invariably by

place in the bowel in the course of such diseases as sprue, pellagra, and Addisonian pernicious anemia. Cowgill<sup>15</sup> considers that the presence of adequate amounts of vitamin B may be of great importance to the normal functioning of the intestinal tract. An indication of the effect of restricted diet is reflected by the recent studies of Miller and Rhoads.<sup>16</sup> They fed a modified canine-black-tongue-producing diet to swine and produced oral mucous membrane lesions, achlorhydria and a loss of the antipernicious anemia activity of the gastric secretion together with a blood picture which resembled that of pernicious anemia.

Hasty conclusions are unwise in this difficult field. It does not seem illogical, however, to consider that a vicious circle is common in many of the chronic deficiency states. The vicious circle may be stated as follows: inadequate dietary intake of certain necessary substances leads to anatomical or physiological changes within the intestine and then to diminished absorption of necessary substances, which in turn lead to further disorder of the intestinal function. The factors of race, age, inheritance, changes of the glands of internal secretion, climate may all play a rôle in the etiology of particular kinds of gastro-intestinal disorders leading to deficiency disease. The exact part which they play is impossible to define at the present time.

**Methods of Clinical Study of the Rate of Absorption.**  
—The conditions affecting the normal rate of absorption being so many and varied, it is impossible to draw far-reaching conclusions from any one method of testing the rate of absorption. Surgical operative measures, moreover, which are of great value in animal experimentation, are not open to the clinician, except by chance in rare cases. Nevertheless, certain methods of clinical study have been in use. Some of these methods are: the glucose tolerance test which has been used in cases of chronic diarrhea; the study of the motility of the bowel;<sup>17</sup> the transference of weight to distant parts of the body after the ingestion of water;<sup>18</sup> the physiological effects of ingested drugs; allergic skin reactions to ingested protein;<sup>19</sup> and the rate of excretion of dyes in the urine.<sup>20</sup> Singer and Wechsler<sup>21</sup> found that, when the galactose toler-

ance test was performed upon patients with anemia and achlorhydria, no galactose appeared in the urine.

The author, working with Fullerton<sup>22</sup> studied a variety of cases in which it was thought that some disturbance of intestinal absorption might be present, including cases of achlorhydria with and without anemia, infections, cirrhosis of the liver, myxedema and scurvy. It was found that the ingestion of water and its excretion in the urine depended upon so many variable factors that it was not of value. The same was found true of the ingestion of glycine and the subsequent determinations of the amino-acid nitrogen content of the blood. Employing a method which has been used by Thienes and Hockett,<sup>23</sup> they administered 0.25 Gm. of potassium iodide in dilute solution and determined the time of the first appearance of iodine in the sputum. In normal individuals, iodine first appeared in the sputum in from ten to fifteen minutes. In most of the cases the time of the first appearance of iodine was delayed significantly. As the patients improved, the time of the first appearance shortened and approached or reached the normal time. The appearance time of iodine after the administration of potassium iodide intravenously, by means of which the influence of the intestine was avoided, was similar in normal subjects and patients. It was therefore believed that delay in the appearance of iodine in the sputum after the ingestion of potassium iodide was a rough measure of disturbance of intestinal absorption.

These methods of studying absorption may be classified as indirect and there are quite obvious objections to many of them. A new technic, which offers the possibility of studying the rate of absorption by a direct method in man has been presented by Miller and Abbott.<sup>24</sup> This technic, which makes use of multiple lumen tubes passed into any desired part of the gastro-intestinal tract seems to offer a distinct advantage over indirect methods. It cannot be considered of value for routine use but will undoubtedly help to unravel certain problems regarding human intestinal absorption.

**Treatment of Disordered Intestinal Function Inhibiting Absorption.**—The advantage to be gained by a good method of testing the rate of intestinal absorption would be not only to detect diminution of the absorption rate in dis-

place in the bowel in the course of such diseases as sprue, pellagra, and Addisonian pernicious anemia. Cowgill<sup>15</sup> considers that the presence of adequate amounts of vitamin B may be of great importance to the normal functioning of the intestinal tract. An indication of the effect of restricted diet is reflected by the recent studies of Miller and Rhoads.<sup>16</sup> They fed a modified canine-black-tongue-producing diet to swine and produced oral mucous membrane lesions, achlorhydria and a loss of the antipernicious anemia activity of the gastric secretion together with a blood picture which resembled that of pernicious anemia.

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**Treatment of Disordered Intestinal Function Inhibiting Absorption.**—The advantage to be gained by a good method of testing the rate of intestinal absorption would be not only to detect diminution of the absorption rate in dis-



orders of the intestine, but also to aid in evaluating methods of treatment when such conditions existed. Very little, however, is accurately known of this subject. Recovery of the papillae of the tongue, improvement in the appearance of the mucosa of the stomach, and improvement of the appetite have been observed in various sorts of anemia associated with dietary deficiency following therapy with iron or liver extract. Spies,<sup>25</sup> among other physicians, has observed healing of mouth lesions and control of diarrhea in the treatment of pellagra with large doses of liver extract parenterally. Improvement of lingual changes and of diarrhea in sprue by the parenteral administration of liver extract also have been noted.<sup>10</sup> Such improvement is very likely associated with a definite return toward normal of the accompanying pathology or altered physiology of the intestine. Large doses of a deficient factor, if necessary parenterally, therefore, are indicated when disorder of the intestine is associated with nutritional deficiency. The aim should be to detect nutritional deficiency early and before permanent damage to the bowel results. By being alert, one may perhaps recognize subjects susceptible to such disorders of the gastro-intestinal tract which might lead to deficiency disease, and thus preventive measures could be applied which undoubtedly would accomplish the most. From our present knowledge, preventive measures would consist largely in the choice of an optimal diet adjusted nicely in respect to all its constituents, having in mind the health of the body as a whole and the gastro-intestinal tract in particular.

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# CUMULATIVE INDEX

- ABDOMINAL distention in pneumonia, treatment, *July*, 13  
 Hodgkin's disease, *Sept.*, 423-427  
 pain, clinical significance and relief, *Jan.*, 1113-1129  
   in children, *March*, 1603-1615  
   severe, following emotional storm, *Sept.*, 399-402  
 paracentesis in congestive failure, *March*, 1570  
 trauma, psychic effect, *Nov.*, 837-845  
 Abortion, habitual, *Nov.*, 829; *March*, 1450  
   threatened, *March*, 1666, 1667  
 Abscess, Bezold's, *Jan.*, 1045  
   of Bartholin's gland in gonorrhea, *Nov.*, 919  
   of brain, eye symptoms, *Jan.*, 1214  
   of lung, bronchial obstruction in, *Sept.*, 456, 462  
   complicating pneumonia, *July*, 33, 34  
   parapharyngeal, *Jan.*, 1152  
   pelvic, gonorrheal, *Nov.*, 921  
   subperichondrial, *Jan.*, 1051  
   suburethral, gonorrheal, *Nov.*, 922  
 Absorption, gastro-intestinal, clinical factors, *March*, 1685-1693  
 Acetyl- $\beta$ -methylcholine in arterial hypertension, *March*, 1351  
   in paroxysmal tachycardia, *Nov.*, 860  
 Acetylcholine in arterial hypertension, *March*, 1350  
 Achlorhydria in conditions other than pernicious anemia, *July*, 48  
 Achlorhydric anemia, simple, *July*, 69  
 Acidosis, diabetic, in children, prevention, *July*, 279  
 Acrodynia, *Nov.*, 957  
 Acromegaly, *Nov.*, 822-824  
 Addison's disease, diagnosis and treatment, *Sept.*, 383-398  
   salt therapy, *Nov.*, 959-965  
 Addisonian anemia. See *Anemia, pernicious*.  
 Adenitis, abdominal, in children, *March*, 1612  
   cervical, in scarlet fever, treatment, *March*, 1395  
 Adenosine in arterial hypertension, *March*, 1351  
 Adenylic acid in arterial hypertension, *March*, 1351  
 Adiposogenital dystrophy, *Nov.*, 826-830  
 Adrenalin in hay fever and asthma, *March*, 1476  
 Adson-Brown operation for hypertension, *March*, 1359  
 Agranulocytic angina, *July*, 103-122  
 Air embolism in artificial pneumothorax, *Nov.*, 908  
 Albuminuric retinitis, *Jan.*, 1236  
 Alcohol in production of pellagra  
   *July*, 60  
   of sprue, *July*, 63  
   injection in glossopharyngeal neuralgia, *Jan.*, 1029  
   in occipital neuralgia, *Jan.*, 1030  
   in superior laryngeal neuralgia, *Jan.*, 1029  
   in trigeminal neuralgia, *Jan.*, 1018-1027  
   intraspinal, for pelvic pain, *Jan.*, 1133  
   paravertebral, for angina pectoris, *March*, 1330  
   use of, in angina pectoris, *Nov.*, 884; *Jan.*, 1104  
 Alcoholic neuritis, *July*, 68; *Nov.*, 951  
 Alcoholism, acute, convulsions in, *July*, 244  
 Alkyl nitrates in arterial hypertension, *March*, 1347  
 Allergic cleanliness, *March*, 1481  
 Allergy, *March*, 1467  
   in children, abdominal pain in, *March*, 1612  
 Alopecia areata, *Jan.*, 1242; *March*, 1631  
 Amenorrhea, *March*, 1453  
 Amidopyrine in causation of agranulocytic angina, *July*, 110-118  
 Aminophyllin in heart disease, *March*, 1321  
 Amputation of cervix in gonorrhea, *Nov.*, 917  
 Amyl nitrite in angina pectoris, *Jan.*, 1099

- Amyloid nephrosis, proteosuria in, *July*, 177-184  
 Amyloidosis, Congo red test, *July*, 179  
 Anemia, achlorhydric, simple, *July*, 69  
   *addisonian*. See *Anemia, pernicious*.  
   after gastrectomy and gastro-ent-  
   terostomy, *July*, 67  
   deficiency, *July*, 37  
   Dibothriocephalus latus, *July*, 64,  
   65  
   hypochromic, idiopathic, *July*, 69,  
   72  
   in inoperable cancer, treatment,  
   *July*, 201  
   in rheumatoid arthritis, treatment,  
   *March*, 1372  
   intestinal malabsorption and,  
   *March*, 1689  
   macrocytic, *July*, 38  
   tropical, *July*, 66  
   with mechanical defects in gastro-  
   intestinal tract, *July*, 67  
   microcytic, *July*, 59, 69  
   nutritional, *July*, 37-77  
   of pregnancy, *July*, 39, 65  
   pernicious, *July*, 37-59; *March*, 1496  
   as deficiency disease, *Sept.*, 469  
   comparison with pernicious leuko-  
   penia, *July*, 105  
   neurological manifestations and  
   their treatment, *July*, 79-89  
   secondary, classification, *July*, 91  
   treatment, *July*, 91-101  
 Angina, agranulocytic, *July*, 103-122  
 pectoris in gallbladder disease, *Nov.*,  
   654  
   pain simulating, *Jan.*, 1077  
   treatment, *Nov.*, 880-887; *Jan.*,  
   1085-1111; *March*, 1321, 1330,  
   1333  
 Anorexia in inoperable cancer, treat-  
   ment, *July*, 197  
 Antitoxin, diphtheria, therapeutic use,  
   *March*, 1401  
   meningococcus, *March*, 1423  
   scarlet fever, *Jan.*, 1285; *March*,  
   1389  
   staphylococcus, *March*, 1426  
   tetanus, *Jan.*, 1284  
 Antophysin, *Nov.*, 818  
 Antuitrin, *Nov.*, 818  
 Aorta and its larger branches, em-  
   bolism and thrombosis of, *July*, 159-  
   170  
 Aortic regurgitation, murmurs of,  
   *March*, 1513  
   stenosis, calcareous, *Sept.*, 487-497  
 Appendicitis, acute, atypical, diag-  
   nosis, *July*, 185-194  
   in children, *March*, 1606  
 Appendicitis in scarlet fever, treat-  
   ment, *March*, 1398  
   pain in, *Jan.*, 1122, 1124  
 Apple diet in diarrhea of infants and  
   children, *July*, 301-305  
 Arm, epitheliomas of, simulating en-  
   dothelioma, sarcoma and sporo-  
   trichosis, *Sept.*, 605-610  
 Arrhythmia in gallbladder disease,  
   *Nov.*, 658  
 Arsenic in treatment of secondary an-  
   emias, *July*, 99  
 Arsenical neuritis, *Nov.*, 955  
 Arterial hypertension, treatment,  
   *July*, 133-149; *March*, 1343-1365  
 Arterial hypotension, *Nov.*, 865-871  
 Arteriosclerosis associated with hy-  
   pertension, *July*, 139  
   eye symptoms, *Jan.*, 1209  
 Arteriosclerotic retinitis, *Jan.*, 1210  
 Arteriovenous fistula, congenital,  
   *Sept.*, 525-533  
 Arthritis, acute, convalescence from,  
   management, *March*, 1374  
   chronic infectious, fever therapy in,  
   *Sept.*, 590  
   inactivation by jaundice, *Sept.*,  
   573-583  
   relief by cholecystostomy and  
   cholecystectomy, *Nov.*, 697  
   gonorrheal, fever therapy, *Sept.*,  
   559, 589; *March*, 1369  
   treatment, *March*, 1368-1370  
   menopausal, *July*, 218  
   of feet, pain in, *Jan.*, 1071  
   postoperative, acute, identification  
   of, *Sept.*, 560-566  
   prevention and treatment,  
   *Sept.*, 566-573  
   rheumatoid, treatment, *March*,  
   1370-1375  
 Arthrodesis for sciatic pain, *Jan.*, 1038  
 Aschheim-Zondek test, *March*, 1452  
 Ascorbic acid, *Sept.*, 482  
 Asthenia, neurocirculatory, *March*,  
   1534-1545  
 Asthma, diagnosis and treatment,  
   *March*, 1467-1492  
   fever therapy, *Sept.*, 591  
   stimulating tracheal and bronchial  
   obstruction, *Sept.*, 453  
 Atelectasis, massive, *Sept.*, 457  
 Aural vertigo, *March*, 1619  
 Auricle of ear, pain in, relief, *Jun.*,  
   1050-1054  
 Auricular fibrillation, *Sept.*, 511-515  
   quinidine therapy, *March*, 1325  
 Austin-Flint murmur, *March*, 1515  
 Autohemotherapy in pruritus, *Nov.*,  
   982  
 Autovaccination, *Jan.*, 1280

- BACILLUS diphtheriae, rapid culture method, *Nov.*, 736
- Backache, relief of, *Jan.*, 1033-1038
- Barbiturates as soporifics, *March*, 1600
- Bartholin's gland, gonorrheal abscess, *Nov.*, 919
- Basedow's disease, eye symptoms, *Jan.*, 1204
- Basophilism, pituitary, *Nov.*, 831
- Beard, ringworm of, *March*, 1638
- Bed-wetting, *July*, 287
- Beriberi, *July*, 68
- in gastro-intestinal disease or abnormality, *Sept.*, 468, 469
- vitamin deficiency in, *Sept.*, 481
- Bezold's abscess, *Jan.*, 1045
- Bile, laboratory study, *Nov.*, 680-684
- pigment in secondary anemias, *July*, 100
- Biliary calculi. See *Cholelithiasis*.
- colic, *Nov.*, 642; *Jan.*, 1118, 1124
- disease following cholecystectomy for stones, *Nov.*, 689
- drainage, nonsurgical, *Nov.*, 677-688
- dyskinesia, *Nov.*, 669, 673
- Biopsy, endometrial, *March*, 1440
- Birth injuries, cerebral, convulsions due to, *July*, 249, 254
- corrective motor education in, *Nov.*, 807-815
- Bismuth subnitrate in arterial hypertension, *March*, 1348
- Black dot of scalp, *Jan.*, 1248
- tongue, *July*, 59
- Bladder neck masses, gonorrheal, *Nov.*, 924
- Blastomycosis, of skin, *March*, 1646
- cutaneous tuberculosis simulating, *Sept.*, 613, 617
- Blood, cholesterol determinations, *Jan.*, 1167
- clotting function, diets to increase and decrease, *Nov.*, 989-999
- dyscrasia, atypical, jaundice arising from, *Sept.*, 545-550
- in relation to bone marrow failure, *March*, 1525
- Bone, giant-cell tumor, roentgen treatment, *Sept.*, 601
- marrow failure, sequence of events in, clinical importance, *March*, 1525-1531
- Braun, abscess, eye symptoms, *Jan.*, 1214
- defects, congenital, convulsions due to, *July*, 251, 254
- tumors, eye symptoms, *Jan.*, 1217
- gastro-intestinal manifestations, *Jan.*, 1260
- headache in, *Jan.*, 1203
- Brain, tumors, pain about oral cavity in, *Jan.*, 1065
- Breast conditions, treatment, *March*, 1451
- Breath, uremic, *July*, 237
- Brodie's serum in poliomyelitis prophylaxis, *Nov.*, 742
- Bronchiectasis, abdominal pain in, *Jan.*, 1116
- treatment, *Jan.*, 1171
- Bronchopneumonia, tuberculous, in children, *Nov.*, 717, 718
- Bronchus, obstruction of, clinical and bronchoscopic findings, *Sept.*, 453-462
- Burning tongue, *Jan.*, 1065
- CALCAREOUS aortic stenosis, *Sept.*, 487-497
- Calcium bilirubin masses in bile, *Nov.*, 681
- Calculus, biliary. See *Cholelithiasis*.
- Carbon monoxide polyneuritis, *Nov.*, 958
- Carcinoma, inoperable, treatment, *July*, 195-204
- multiple, complicating chronic ulcerative colitis, *Sept.*, 408-410
- of bronchus causing obstruction, *Sept.*, 455
- of cervical stump after hysterectomy, *Sept.*, 352
- of cervix, diagnosis, *March*, 1443
- incidence, *Sept.*, 350
- pain in, relief, *Jan.*, 1133
- of colon, cooperative management, *Sept.*, 619, 621, 625
- of kidney, roentgen treatment, *Sept.*, 601
- of lungs, bronchial obstruction in, *Sept.*, 456
- of skin, roentgen treatment, *Sept.*, 599
- of small intestine, *Sept.*, 366
- of thyroid gland, roentgen treatment, *Sept.*, 600
- roentgen therapy, *Sept.*, 598-603
- Cardiac neurosis, *March*, 1533
- Cardiospasm in gallbladder disease, *Nov.*, 653
- Carotene, *Sept.*, 479
- Carotid sinus dizziness and syncope, *March*, 1624
- Caruncle, urethral, *Nov.*, 923
- Cataract, diabetic, *Jan.*, 1232
- Catarrhal jaundice, biliary drainage in, therapeutic value, *Nov.*, 685
- Cauterization of cervix for cervicitis, *Sept.*, 354
- in gonorrhea, *Nov.*, 915, 918

- Cerebral accidents, coma of, treatment, *Jan.*, 1270  
 birth injuries, convulsions due to, *July*, 249, 254  
 corrective motor education in, *Nov.*, 807-815  
 Cerumen, impacted, *Jan.*, 1052  
 Cervical adenitis in scarlet fever, treatment, *March*, 1395  
 stump, carcinoma of, following hysterectomy, *Sept.*, 352  
 Cervicitis, *Sept.*, 349  
 cautery treatment, *Sept.*, 354; *Nov.*, 915, 918  
 Elliott heat treatment, *Sept.*, 353  
 Cervix uteri, amputation of, in gonorrhea, *Nov.*, 917  
 carcinoma of, diagnosis, *March*, 1443  
 pain in, relief, *Jan.*, 1133  
 erosion, congenital, *March*, 1441  
 gonorrhea of, treatment in nulliparous, *Nov.*, 918  
 in parous, *Nov.*, 914  
 lesions of, *Sept.*, 347-357  
 Cevitamic acid, *Sept.*, 482  
 Chickenpox, immunization, *Jan.*, 1290  
 Children, diseases of, symposium on, *Nov.*, 701  
 Chloral as soporific, *March*, 1599  
 Choked disk in brain abscess, *Jan.*, 1215  
 in brain tumor, *Jan.*, 1217  
 Cholangitis, *Nov.*, 665  
 biliary drainage in, therapeutic value, *Nov.*, 687  
 Cholecystectomy for stones, biliary disease following, *Nov.*, 689  
 relief of chronic arthritis by, *Nov.*, 697  
 Cholecystitis, chronic, diagnosis, *Nov.*, 641-648  
 lenta, *Nov.*, 665  
 Cholecystography, *Nov.*, 644  
 Cholecystopathica spastica, *Nov.*, 670  
 Cholecystostomy, relief of chronic arthritis by, *Nov.*, 697  
 Cholelithiasis, cholecystectomy for, biliary disease following, management, *Nov.*, 689  
 diagnosis, *Nov.*, 641-648  
 Cholesterol in crystals in bile, *Nov.*, 681  
 Cholesterol in blood, determinations, *Jan.*, 1167  
 Chordotomy for pelvic pain, *Jan.*, 1140  
 Chorea in children, fever therapy, *Sept.*, 591; *Nov.*, 771-784  
 Choreo-athetosis, *Nov.*, 808, 809  
 Chvostek's sign in tetany, *July*, 242, 255  
 Cinchophen in acute postoperative gout, *Sept.*, 570  
 Climacteric. See *Menopause*.  
 Clotting function of blood, diets to influence, *Nov.*, 989-999  
 Cold test in hypertension, *Sept.*, 518  
 Colds, common, *March*, 1499-1504  
 in infants and children, *Nov.*, 745-750  
 Colic, biliary, *Nov.*, 642; *Jan.*, 1118, 1124  
 in infants, *March*, 1609  
 renal, *Jan.*, 1119, 1124  
 Colitis in children, *March*, 1608  
 mucous, *Jan.*, 1123, 1128  
 ulcerative, chronic, management, *Sept.*, 403-407  
 two carcinomas complicating, *Sept.*, 408-410  
 idiopathic, in children, *March*, 1673-1683  
 regional, *Sept.*, 411-422  
 Colon, carcinoma of, cooperative management, *Sept.*, 619, 621, 625  
 disturbances in gallbladder disease, *Nov.*, 662, 663  
 irritable, pain in, *Jan.*, 1123, 1127  
 spastic, in children, *March*, 1608  
 Colposcopy, *March*, 1443  
 Coma, diabetic. See *Diabetic coma*.  
 treatment, *Jan.*, 1265-1271  
 Communicable diseases, recent developments, *Nov.*, 731-744; *Jan.*, 1277-1290  
 Complement fixation test in tuberculosis in children, *Nov.*, 724  
 Congestive heart failure, management, *March*, 1563-1570  
 Congo red test in amyloidosis, *July*, 179  
 Conization in gonorrhea of cervix, *Nov.*, 914  
 Constipation in pregnancy, *March*, 1664  
 Convalescent serum in measles, *Jan.*, 1288  
 in poliomyelitis, *Jan.*, 1290  
 in scarlet fever, *March*, 1393  
 Convulsions, *July*, 233-246  
 epileptic, *July*, 259-264; *March*, 1583-1595  
 epileptiform, *July*, 260  
 in children, diagnosis and treatment, *July*, 247-265  
 jacksonian, *July*, 260  
 Copper in treatments of secondary anemias, *July*, 99  
 Corns, *Jan.*, 1072  
 Coronary disease, pain simulating, *Jan.*, 1077-1083  
 occlusion, abdominal pain in, *Jan.*, 1116

- Coronary occlusion, acute, *Sept.*, 499-510  
     seasonal incidence in Philadelphia, *July*, 151-157  
     thrombosis, angina pectoris and, differentiation, *Jan.*, 1085  
     treatment, *Nov.*, 873-880, 887  
 Cryptococcosis epidermica, *March*, 1640  
 Cucurbititrin in arterial hypertension, *March*, 1352  
 Culture medium, Löwenstein's, in tuberculosis, *Nov.*, 722  
 Cutaneous. See *Skin*.  
 Cysts, nabothian, *Sept.*, 349  
     tubal, in female gonorrhea, *Nov.*, 920
- DALRYMPLE's sign, *Jan.*, 1208  
 Deficiency anemias, *July*, 37  
     diseases, intestinal absorption in, *March*, 1688  
     methods of production, *Sept.*, 468  
     occurrence of, *Sept.*, 466, 474  
 Dehydration in inoperable cancer, treatment, *July*, 202  
 Delirium in pneumonia, treatment, *July*, 14  
 Denervation of kidney for hypertension, *March*, 1359  
     of suprarenal glands for hypertension, *March*, 1358  
 Dental field, pain in, *Jan.*, 1057-1066  
 Dermatomycosis, *March*, 1641  
 Dermatopolymyneuritis, *Nov.*, 957  
 Dermatoses, pruritus of, *Nov.*, 979  
 Deryl-Hart apparatus, *July*, 31  
 Desensitization in hay fever and asthma, *March*, 1483, 1555  
 Diabetes, abdominal pain in, *March*, 1613  
     eye symptoms, *Jan.*, 1231  
     in children, insulin in, *Nov.*, 791-805  
     management, *July*, 273-286  
 Diabetic coma in children, treatment, *Nov.*, 800  
     treatment, *Jan.*, 1268  
     polyneuritis, *Nov.*, 956  
 Diagnostic methods, new, in gynecology, *March*, 1439  
 Diaphragmatic hernia, anginal pain in, *Jan.*, 1083  
     pleurisy, abdominal pain in, *Jan.*, 1115  
 Diarrhea of infants and children, apple diet in, *July*, 301-305  
 Diastolic murmurs, *March*, 1513  
 Diathermy in gonorrhea of cervix, *Nov.*, 914  
 Diathesis, exudative, *July*, 326
- Dibothriocephalus latus anemia, *July*, 64, 65  
 Dick test, *Jan.*, 1285  
 Diet, apple, in diarrhea of infants and children, *July*, 301-305  
     "bleeding" and "clotting," *Nov.*, 989-999  
 Diabetic, for children, *July*, 274  
     elimination, in hay fever and asthma, *March*, 1482, 1490  
     in angina pectoris, *Jan.*, 1097  
     in congestive heart failure, *March*, 1564  
     in coronary thrombosis, *Nov.*, 876, 887  
     in pneumonia, *July*, 15, 17  
     in pregnancy, *March*, 1663, 1668  
     in rheumatoid arthritis, *March*, 1371  
     Karell, *July*, 174  
     ketogenic, in epilepsy, *July*, 263  
 Dietary treatment of hypertension, *July*, 144; *March*, 1353  
     of inoperable cancer, *July*, 197  
     of nephritis with vascular and cardiac complications, *July*, 175  
     of secondary anemias, *July*, 97  
     recent advances, *March*, 1493-1498  
 Digitalis in congestive heart failure, *March*, 1566  
     in nephritis with vascular and cardiac complications, *July*, 174  
 Digitalization in pneumonia, *July*, 14  
 Diphtheria antitoxin, therapeutic use, *March*, 1401  
     bacillus, rapid culture method, *Nov.*, 736  
     Schick test, *Jan.*, 1282  
     toxoid for immunization, *Nov.*, 736; *Jan.*, 1281  
     treatment, *March*, 1401-1406  
     with heart involvement, *Nov.*, 737  
 Diphtheritic polyneuritis, *Nov.*, 955  
 Diuretics in congestive heart failure, *March*, 1568  
     in nephritis with vascular and cardiac complications, *July*, 174  
 Diverticula, Meckel's, *Sept.*, 372, 373  
     of small intestine, *Sept.*, 372  
 Diverticulitis, *Sept.*, 374  
     perforation in, management, *Sept.*, 407  
 Dizziness, significance and treatment, *March*, 1617, 1621-1626  
 Drugs, convulsant, poisoning in children by, *July*, 256  
     in causation of pernicious leukopenia, *July*, 110-118  
     poisoning by, treatment, *Jan.*, 1268  
 Ductus arteriosus, patent, *March*, 1517



- Duroziez's sign, *March*, 1513  
 Dwarfism, pituitary, *Nov.*, 825, 826  
 Dysinsulinism, *July*, 233  
 Dyskinesia, biliary, *Nov.*, 669, 673  
 Dysmenorrhea, *Jan.*, 1132; *March*, 1456  
 Dyspareunia, *July*, 267, 268  
 Dyspepsia in gallbladder disease, *Nov.*, 642  
 Dystrophy, adiposogenital, *Nov.*, 826-830
- EAR drops, *Jan.*, 1042  
   drum, blue, *Jan.*, 1048  
   paracentesis of, *Jan.*, 1042  
   rupture of, traumatic, *Jan.*, 1054  
   foreign bodies in, pain due to, *Jan.*, 1052  
 Earache, reflex, *Jan.*, 1054  
   treatment, *Jan.*, 1039-1055  
 Eclampsia, threatened, *March*, 1669, 1670  
 Eclamptic uremia, acute, *July*, 236, 238  
 Ectropion of cervix, *Sept.*, 349  
 Eczema, contact, *July*, 319-324  
   in infancy and childhood, *July*, 325-331  
   mycoticum, *March*, 1641  
   of ear, *Jan.*, 1050  
 Edema, stasis, in thrombophlebitis, *Sept.*, 542  
   in varicose veins, *Sept.*, 538  
 Elimination diet in hay fever and asthma, *March*, 1482, 1490  
 Elliott heat treatment of cervicitis, *Sept.*, 353  
 Embolectomy, *July*, 168  
 Embolism, air, in artificial pneumothorax, *Nov.*, 908  
   of aorta and its larger branches, *July*, 159-170  
   pulmonary, simulating coronary disease, *Jan.*, 1079  
 Embryoma of testis, *Sept.*, 599  
 Emotional factors in epilepsy, *March*, 1591, 1594  
   storm, severe abdominal pains following, *Sept.*, 399-402  
 Empyema complicating pneumonia, surgical management, *July*, 30-33  
   in scarlet fever, treatment, *March*, 1398  
 Encephalitis, epidemic, eye symptoms, *Jan.*, 1228  
   postvaccinal, *Jan.*, 1280  
 Encephalopathy, hypertensive, *July*, 238  
 Endocarditis in scarlet fever, treatment, *March*, 1397
- Endocrine therapy. See *Hormone therapy*.  
 Endometrial biopsy, *March*, 1440  
 Enterocolitis, ulcerative, regional, *Sept.*, 411-422  
 Enuresis in childhood, causes and treatment, *July*, 287-294  
 Ephedrine in hay fever and asthma, *March*, 1478  
 Epidermophytide, *March*, 1644  
 Epidermophytosis, *March*, 1641  
 Epilepsy, *July*, 259-264; *March*, 1583-1595  
 Epileptiform convulsions, *July*, 260  
 Epiphyses, separation of, *Nov.*, 830  
 Epitheliomas of arm simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610  
   of ear, *Jan.*, 1054  
 Epituberculosis, roentgen findings, *Nov.*, 715  
 Erb's sign in tetany, *July*, 255  
 Erosio interdigitalis, *March*, 1644  
 Erosion of cervix, *Sept.*, 349  
   cautery treatment, *Sept.*, 354  
   congenital, *March*, 1441  
 Erysipelas of auricle, *Jan.*, 1051  
 Erythematous lupus, visceral lesions of, *July*, 333-346  
 Erythrasma, *March*, 1649  
 Erythredema polyneuritis, *Nov.*, 957  
 Estrin, *March*, 1462  
   in amenorrhea, *March*, 1454  
   in dysmenorrhea, *March*, 1457  
   in menopause, *July*, 220-224; *March*, 1462  
   in urine, test, *March*, 1440  
 Ethyl iodide inhalations in epidermophytosis, *March*, 1643  
   in tinea, *March*, 1637  
 Evaporated milk for infants, *Nov.*, 787  
 Eversion of cervix, *Sept.*, 349  
 Ewing's tumor, roentgen therapy, *Sept.*, 602  
 Exophthalmic goiter, eye symptoms, *Jan.*, 1204  
 Extremities, increased length in arteriovenous fistula, *Sept.*, 526, 528  
   venous diseases, *Sept.*, 545, 548  
 Exudative diathesis, *July*, 326  
 Eyegrounds examination, *Jan.*, 1193  
 Eyes, examination, *Jan.*, 1189  
   in acute disseminated lupus erythematosus, *July*, 337  
   symptoms diagnostic value in peroral disease, *Jan.*, 1187, 1239  
 Eyestrain, headache due to, *Jan.*, 1292

- Fainting attacks, *March*, 1622  
 Favus of scalp, *Jan.*, 1249; *March*, 1636  
 Febrile diseases in infants, convulsions due to, *July*, 252  
 Feeding, infant, difficult cases, *Nov.*, 785-789  
 Feet, painful, relief of, *Jan.*, 1067-1075  
 Ferments, pancreatic, *Nov.*, 683  
 Ferry's meningococcus antitoxin, *March*, 1423  
 Fever in acute appendicitis, *July*, 193  
   therapy, *Sept.*, 585-595  
     in chorea in children, *Sept.*, 591; *Nov.*, 771-784  
     in gonococcal arthritis, *Sept.*, 551-559, 589; *March*, 1369  
     in rheumatoid arthritis, *March*, 1372  
 Fibrositis, chronic, inactivation by jaundice, *Sept.*, 573-583  
 Fistula, arteriovenous, congenital, *Sept.*, 525  
   gastrojejunocolic, anemia with, *July*, 67  
     of small intestine, *Sept.*, 377  
 Fits, *March*, 1583-1595  
 Flush, menopausal, *July*, 215  
 Foci of infection, removal in arthritis, *March*, 1371  
 Follutein, *Nov.*, 818  
 Foods, vitamin content, advisability of increasing, *Sept.*, 472  
 Foot, march, *Jan.*, 1075  
   strain, *Jan.*, 1073  
 Foreign bodies in bronchus causing obstruction, *Sept.*, 457  
   in ear, pain due to, *Jan.*, 1052  
 Fractures of ribs, pain in, simulating coronary disease, *Jan.*, 1081  
   of skull, eye symptoms, *Jan.*, 1238  
 Friction rubs, pericardial, *March*, 1516  
 Friedman test, *March*, 1452  
 Frigidity in female, *March*, 1448  
 Frohlich's syndrome, *Nov.*, 826-830  
 Frostbite of ear, *Jan.*, 1053  
 Fundus, eye, examination, *Jan.*, 1201  
 Fungi in external ear, *Jan.*, 1050  
 Fungus diseases of skin, *March*, 1633  
 Furunculosis of ear, *Jan.*, 1049
- GALLBLADDER disease, metabolic disturbances in, *Nov.*, 664  
   pancreatic disease associated with, *Nov.*, 664  
   symposium on, *Nov.*, 639  
   symptoms, atypical, *Nov.*, 649-675  
   dyskinesia, *Nov.*, 669, 673  
   functional disturbances, *Nov.*, 666  
     treatment, *Nov.*, 672  
   stasis, *Nov.*, 669  
   vertigo, *Nov.*, 653  
 Gallstones. See *Cholelithiasis*.  
 Gas pains, postoperative, *Jan.*, 1125  
 Gasserian ganglion, sensory root avulsion, for trigeminal neuralgia, *Jan.*, 1028  
 Gastrectomy, anemia following, *July*, 67  
 Gastric juice in relation to pernicious anemia, *July*, 41  
   lavage for diagnosis of tuberculosis, *Nov.*, 721  
   resection for peptic ulcer, recurrences after, *Sept.*, 451  
   tetany, *July*, 242  
 Gastroduodenostomy, lateral, for peptic ulcer, recurrence after, *Sept.*, 434  
 Gastro-enterostomy for peptic ulcer, recurrent and anastomotic ulcer after, *Sept.*, 441  
 Gastro-intestinal manifestations of systemic disease and their differential diagnosis, *Jan.*, 1251-1263  
 Gastrojejunal ulcer following gastroenterostomy, *Sept.*, 442  
   tract, absorption in, clinical factors, *March*, 1685-1693  
   in development of deficiency diseases, *Sept.*, 468  
 Gastrojejunocolic fistula, anemia with, *July*, 67  
 Gastrotomy, anemia following, *July*, 67  
 Giant-cell tumor of bone, roentgen treatment, *Sept.*, 601  
 Giardia intestinalis in bile, *Nov.*, 680  
 Gifford's sign, *Jan.*, 1208  
 Ginger paralysis, *Nov.*, 953  
 Glaucoma, headache in, *Jan.*, 1203  
 Glomerulonephritis in scarlet fever, treatment, *March*, 1396  
 Glossitis, atrophic, nutritional factors, *July*, 59  
 Glossopharyngeal neuralgia, relief of, *Jan.*, 1028  
 Goiter, exophthalmic, eye symptoms, *Jan.*, 1204  
   toxic, treatment, *March*, 1377  
 Gonadal insufficiencies, pituitary, *Nov.*, 832

- Duroziez's sign, *March*, 1513  
 Dwarfism, pituitary, *Nov.*, 825, 826  
 Dysinsulinism, *July*, 233  
 Dyskinesia, biliary, *Nov.*, 669, 673  
 Dysmenorrhea, *Jan.*, 1132; *March*, 1456  
 Dyspareunia, *July*, 267, 268  
 Dyspepsia in gallbladder disease, *Nov.*, 642  
 Dystrophy, adiposogenital, *Nov.*, 826-830  
  
 EAR drops, *Jan.*, 1042  
   drum, blue, *Jan.*, 1048  
   paracentesis of, *Jan.*, 1042  
   rupture of, traumatic, *Jan.*, 1054  
   foreign bodies in, pain due to, *Jan.*, 1052  
 Earache, reflex, *Jan.*, 1054  
   treatment, *Jan.*, 1039-1055  
 Eclampsia, threatened, *March*, 1669, 1670  
 Eclamptic uremia, acute, *July*, 236, 238  
 Ectropion of cervix, *Sept.*, 349  
 Eczema, contact, *July*, 319-324  
   in infancy and childhood, *July*, 325-331  
   mycoticum, *March*, 1641  
   of ear, *Jan.*, 1050  
 Edema, stasis, in thrombophlebitis, *Sept.*, 542  
   in varicose veins, *Sept.*, 538  
 Elimination diet in hay fever and asthma, *March*, 1482, 1490  
 Elliott heat treatment of cervicitis, *Sept.*, 353  
 Embolectomy, *July*, 168  
 Embolism, air, in artificial pneumothorax, *Nov.*, 908  
   of aorta and its larger branches, *July*, 159-170  
   pulmonary, simulating coronary disease, *Jan.*, 1079  
 Embryoma of testis, *Sept.*, 599  
 Emotional factors in epilepsy, *March*, 1591, 1594  
   storm, severe abdominal pains following, *Sept.*, 399-402  
 Empyema complicating pneumonia, surgical management, *July*, 30-33  
   in scarlet fever, treatment, *March*, 1398  
 Encephalitis, epidemic, eye symptoms, *Jan.*, 1228  
   postvaccinal, *Jan.*, 1280  
 Encephalopathy, hypertensive, *July*, 238  
 Endocarditis in scarlet fever, treatment, *March*, 1397  
 Endocrine therapy. See *Hormone therapy*.  
 Endometrial biopsy, *March*, 1440  
 Enterocolitis, ulcerative, regional, *Sept.*, 411-422  
 Enuresis in childhood, causes and treatment, *July*, 287-294  
 Ephedrine in hay fever and asthma, *March*, 1478  
 Epidermophytide, *March*, 1644  
 Epidermophytosis, *March*, 1641  
 Epilepsy, *July*, 259-264; *March*, 1583-1595  
 Epileptiform convulsions, *July*, 260  
 Epiphyses, separation of, *Nov.*, 830  
 Epitheliomas of arm simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610  
   of ear, *Jan.*, 1054  
 Epituberculosis, roentgen findings, *Nov.*, 715  
 Erb's sign in tetany, *July*, 255  
 Erosio interdigitalis, *March*, 1644  
 Erosion of cervix, *Sept.*, 349  
   cautery treatment, *Sept.*, 354  
   congenital, *March*, 1441  
 Erysipelas of auricle, *Jan.*, 1051  
 Erythematous lupus, visceral lesions of, *July*, 333-346  
 Erythrasma, *March*, 1649  
 Erythredema polyneuritis, *Nov.*, 957  
 Estrin, *March*, 1462  
   in amenorrhea, *March*, 1454  
   in dysmenorrhea, *March*, 1457  
   in menopause, *July*, 220-224; *March*, 1462  
   in urine, test, *March*, 1440  
 Ethyl iodide inhalations in epidermophytosis, *March*, 1643  
   in tinea, *March*, 1637  
 Evaporated milk for infants, *Nov.*, 787  
 Eversion of cervix, *Sept.*, 349  
 Ewing's tumor, roentgen therapy, *Sept.*, 602  
 Exophthalmic goiter, eye symptoms, *Jan.*, 1204  
 Extremities, increased length, in arteriovenous fistula, *Sept.*, 526, 528  
   venous diseases, *Sept.*, 535-543  
 Exudative diathesis, *July*, 326  
 Eyegrounds, examination, *Jan.*, 1198  
 Eyes, examination, *Jan.*, 1189  
   in acute disseminated lupus erythematosus, *July*, 337  
   symptoms, diagnostic value in general disease, *Jan.*, 1187-1239  
 Eyestrain, headaches due to, *Jan.*, 1202  
  
 FACIAL neuralgia, relief of, *Jan.*, 1017-1028

- Fainting attacks, *March*, 1622  
 Favus of scalp, *Jan.*, 1249; *March*, 1636  
 Febrile diseases in infants, convulsions due to, *July*, 252  
 Feeding, infant, difficult cases, *Nov.*, 785-789  
 Feet, painful, relief of, *Jan.*, 1067-1075  
 Ferments, pancreatic, *Nov.*, 683  
 Ferry's meningococcus antitoxin, *March*, 1423  
 Fever in acute appendicitis, *July*, 193  
   therapy, *Sept.*, 585-595  
   in chorea in children, *Sept.*, 591; *Nov.*, 771-784  
   in gonococcal arthritis, *Sept.*, 551-559, 589; *March*, 1369  
   in rheumatoid arthritis, *March*, 1372  
 Fibrositis, chronic, inactivation by jaundice, *Sept.*, 573-583  
 Fistula, arteriovenous, congenital, *Sept.*, 525  
   gastrojejunal, anemia with, *July*, 67  
   of small intestine, *Sept.*, 377  
 Fits, *March*, 1583-1595  
 Flush, menopausal, *July*, 215  
 Foci of infection, removal in arthritis, *March*, 1371  
 Follutein, *Nov.*, 818  
 Foods, vitamin content, advisability of increasing, *Sept.*, 472  
 Foot, march, *Jan.*, 1075  
   strain, *Jan.*, 1073  
 Foreign bodies in bronchus causing obstruction, *Sept.*, 457  
   in ear, pain due to, *Jan.*, 1052  
 Fractures of ribs, pain in, simulating coronary disease, *Jan.*, 1081  
   of skull, eye symptoms, *Jan.*, 1238  
 Friction rubs, pericardial, *March*, 1516  
 Friedman test, *March*, 1452  
 Frigidity in female, *March*, 1448  
 Fröhlich's syndrome, *Nov.*, 826-830  
 Frostbite of ear, *Jan.*, 1053  
 Fundus, eye, examination, *Jan.*, 1201  
 Fungi in external ear, *Jan.*, 1050  
 Fungus diseases of skin, *March*, 1633  
 Furunculosis of ear, *Jan.*, 1049
- GALLBLADDER disease, metabolic disturbances in, *Nov.*, 664  
   pancreatic disease associated with, *Nov.*, 664  
   symposium on, *Nov.*, 639  
   symptoms, atypical, *Nov.*, 649-675  
   dyskinesia, *Nov.*, 669, 673  
   functional disturbances, *Nov.*, 666  
     treatment, *Nov.*, 672  
   stasis, *Nov.*, 669  
   vertigo, *Nov.*, 653  
 Gallstones. See *Cholelithiasis*.  
 Gas pains, postoperative, *Jan.*, 1125  
 Gasserian ganglion, sensory root avulsion, for trigeminal neuralgia, *Jan.*, 1028  
 Gastrectomy, anemia following, *July*, 67  
 Gastric juice in relation to pernicious anemia, *July*, 41  
   lavage for diagnosis of tuberculosis, *Nov.*, 721  
   resection for peptic ulcer, recurrences after, *Sept.*, 451  
   tetany, *July*, 242  
 Gastroduodenostomy, lateral, for peptic ulcer, recurrence after, *Sept.*, 434  
 Gastro-enterostomy for peptic ulcer, recurrent and anastomotic ulcer after, *Sept.*, 441  
 Gastro-intestinal manifestations of systemic disease and their differential diagnosis, *Jan.*, 1251-1263  
 Gastrojejunal ulcer following gastro-enterostomy, *Sept.*, 442  
   tract, absorption in, clinical factors, *March*, 1685-1693  
   in development of deficiency diseases, *Sept.*, 468  
 Gastrojejunal fistula, anemia with, *July*, 67  
 Gastrotomy, anemia following, *July*, 67  
 Giant-cell tumor of bone, roentgen treatment, *Sept.*, 601  
 Giardia intestinalis in bile, *Nov.*, 680  
 Gifford's sign, *Jan.*, 1208  
 Ginger paralysis, *Nov.*, 953  
 Glaucoma, headache in, *Jan.*, 1203  
 Glomerulonephritis in scarlet fever, treatment, *March*, 1396  
 Glossitis, atrophic, nutritional factors, *July*, 59  
 Glossopharyngeal neuralgia, relief of, *Jan.*, 1028  
 Goiter, exophthalmic, eye symptoms, *Jan.*, 1204  
   toxic, treatment, *March*, 1377  
 Gonadal insufficiencies, pituitary, *Nov.*, 832
- GAENSELEN'S sign in sacro-iliac lesions, *Jan.*, 1036  
 Galactose tolerance test, *Jan.*, 1167  
 Gallbladder disease, biliary drainage in, diagnostic, *Nov.*, 679  
   therapeutic value, *Nov.*, 687  
 diagnosis, *Nov.*, 641-648

- Gonococcal arthritis, treatment, *Sept.*, 551-559, 589; *March*, 1368-1370  
 urethritis, fever therapy, *Sept.*, 588  
 Gonorrhea in women, *Nov.*, 911-914  
 treatment, *Nov.*, 914-926  
 Gonorrheal vulvovaginitis in children, *March*, 1445  
 Gout, postoperative, acute, identification of, *Sept.*, 560-566  
 prevention and treatment, *Sept.*, 566-573; *March*, 1375  
 Gradenigo's syndrome, *Jan.*, 1046  
 Graham test in gallbladder disease, errors in interpretation, *Nov.*, 678  
 Grand mal, *July*, 260  
 Granulocytoclastic crisis, *July*, 115  
 Granulomata of ear, *Jan.*, 1054  
 Graves' disease, eye symptoms, *Jan.*, 1204  
 Growth in children, *July*, 307-317  
 Gynecological lesions, pain in, *Jan.*, 1122, 1131  
 Gynecology, medical, recent advances, *March*, 1439-1466
- HALLUX rigidus, *Jan.*, 1074  
 Hartmann's solution in diabetic coma, *Nov.*, 803  
 Hay fever, diagnosis and treatment, *March*, 1467-1492, 1547-1562  
 Head injuries, eye symptoms, *Jan.*, 1238  
 Headache due to migraine, relief of, *Jan.*, 1015  
 eyestrain and, *Jan.*, 1202  
 in brain tumor, *Jan.*, 1203  
 in glaucoma, *Jan.*, 1203  
 menopausal, *July*, 217  
 pituitary, *Nov.*, 833  
 waking, *Jan.*, 1202  
 Heart block, convulsions and unconsciousness in, *July*, 243  
 frequency, *July*, 123-129  
 treatment, *July*, 129-131  
 disease, gastro-intestinal manifestations, *Jan.*, 1261  
 in pregnancy, management, *Nov.*, 893-899  
 organic, neurocirculatory asthenia complicating, *March*, 1543  
 treatment, recent advances, *March*, 1321-1341  
 disorderly action, *March*, 1534  
 failure complicating chronic glomerular nephritis, *July*, 171  
 congestive, management, *March*, 1563-1570  
 involvement in diphtheria, *Nov.*, 737  
 murmurs, significance and interpretation, *March*, 1505-1518
- Heart, pain in region of, *March*, 1533-1545  
 soldier's, *March*, 1534  
 Hegar's sign, *March*, 1661  
 Hemolytic crisis, acute, *Sept.*, 548, 549  
 jaundice, *Sept.*, 545, 549  
 Hemoptysis in pulmonary tuberculosis, management, *Nov.*, 901-904  
 Hepatitis, biliary drainage in, therapeutic value, *Nov.*, 687  
 Hernia, diaphragmatic, anginal pain in, *Jan.*, 1083  
 Herpes zoster of auricle, *Jan.*, 1052  
 Hexuronic acid, *Sept.*, 482  
 Hilar nodes, tuberculous, *Nov.*, 711  
 Hirsutism, *March*, 1442  
 Histamine in arterial hypertension, *March*, 1349  
 Hodgkin's disease, abdominal, *Sept.*, 423-427  
 itching in, treatment, *Nov.*, 967-970  
 Homosexuality, *Nov.*, 938  
 Hormone therapy, female, *March*, 1462  
 in Addison's disease, *Sept.*, 392-396  
 in amenorrhea, *March*, 1453  
 in arterial hypertension, *March*, 1353  
 in breast conditions, *March*, 1451  
 in dysmenorrhea, *March*, 1456  
 in functional metrorrhagia, *Sept.*, 361; *March*, 1459  
 in menopause, *July*, 220, 221; *March*, 1462  
 in pituitary disorders, *Nov.*, 818  
 in secondary anemia, *July*, 100  
 in sterility, *March*, 1449  
 Hormones, urine tests for, *March*, 1440  
 Hunt's zoster auriculæ, *Jan.*, 1052  
 Huntton's antibody solution in pneumonia, *July*, 6  
 Hydrocephalus, convulsions due to, *July*, 251, 254  
 Hydromyelia, *March*, 1577  
 Hydrosalpinx, gonorrheal, *Nov.*, 920  
 Hyperinsulinism, *July*, 233  
 Hypersensitiveness, tests for, *March*, 1471  
 Hypertension, *July*, 133  
 arteriosclerosis with, *July*, 139  
 cold test in, *Sept.*, 518  
 complicating chronic glomerular nephritis, *July*, 171  
 essential, *Sept.*, 517-524  
 familial, *July*, 137; *Sept.*, 517  
 surgery in, *Sept.*, 522; *March*, 1354  
 latent, *Sept.*, 521  
 malignant, *July*, 134

- Hypertension, menopausal, *July*, 216  
treatment, *July*, 133-149; *March*, 1343-1365
- Hypertensive encephalopathy, *July*, 238
- Hypertherm, Kettering, *Sept.*, 585
- Hyperthyroidism, gastro-intestinal manifestations, *Jan.*, 1258
- Hyperventilation tetany, *July*, 242
- Hypochromic anemia, idiopathic, *July*, 69
- Hypoglycemia, *July*, 233  
convulsions of, *July*, 234
- Hypogonadism, pituitary, *Nov.*, 828
- Hypoparathyroid tetany, *July*, 242, 243
- Hypotension, *Nov.*, 865-871
- Hysterectomy, carcinoma of cervical stump following, *Sept.*, 352
- Hysteria, traumatic, *Nov.*, 838, 839
- Hysterical convulsions, *July*, 245  
in children, *July*, 260
- ICTERUS index, *Jan.*, 1166
- Id eruption of scalp, *Jan.*, 1248
- Ititis, regional, *Sept.*, 413
- Ileostomy in ulcerative colitis in children, *March*, 1680
- Ileum, ulcers of, *Sept.*, 380
- Ileus, *Sept.*, 377
- Illumination tests of eye, *Jan.*, 1195, 1197
- Immunity in newborn, *Nov.*, 733
- Immunization against infectious diseases of childhood, *Nov.*, 731-744; *Jan.*, 1277-1290
- Impetigo contagiosa, *March*, 1627  
of newborn, *March*, 1630
- Indigestion, acute, anginal pain in, *Jan.*, 1083  
in children, *March*, 1609
- Infant feeding, difficult cases, *Nov.*, 785-789
- Infantile paralysis. See *Poliomyelitis*.
- Infantilism, pituitary, *Nov.*, 825, 826
- Infections, acute, in infants, convulsions due to, *July*, 251, 252  
resistance to, vitamins and, *Sept.*, 471  
roentgen treatment, *Sept.*, 597
- Infectious diseases of childhood, immunization against, *Nov.*, 731-744; *Jan.*, 1277-1290
- Inflammatory conditions, roentgen treatment, *Sept.*, 597  
disease, pelvic, gonorrheal, *Nov.*, 920
- Inflations in otitis media, *Jan.*, 1042
- Influenzal meningitis, *Nov.*, 768
- Insomnia in hypertension, treatment, *July*, 144
- Insomnia, menopausal, *July*, 218  
treatment, *March*, 1597-1601
- Insulin in diabetes of childhood, *July*, 277; *Nov.*, 791-805
- Intercourse, unsatisfactory, treatment of, *July*, 267
- Intestinal absorption, clinical factors, *March*, 1685  
anastomosis, multiple, macrocytic anemia following, *July*, 67  
obstruction in children, *March*, 1606
- Intestine, small, lesions of, other than peptic ulcer, *Sept.*, 365-382
- Intracranial disease, abdominal pain in, *March*, 1614  
vertigo in, *March*, 1620
- Intradermal skin test, *March*, 1473, 1554
- Intussusception, *Sept.*, 378; *March*, 1605
- Iodine test for carcinoma of cervix, *March*, 1443
- Iron therapy in secondary anemias, *July*, 93-96
- Irritable colon, pain in, *Jan.*, 1123, 1127
- Itching, *Nov.*, 971-980  
in Hodgkin's disease, treatment, *Nov.*, 967-970  
of vulva, *March*, 1445, 1446  
treatment, *Nov.*, 980-987
- JACKSONIAN convulsions, *July*, 260
- Jaeger's test types, *Jan.*, 1193
- Jake paralysis, *Nov.*, 953
- Jaundice, catarrhal, biliary drainage in, therapeutic value, *Nov.*, 685  
diagnosis and medical management, *Jan.*, 1163  
four clinical types arising from atypical blood dyscrasia, *Sept.*, 545-550  
hemolytic, *Sept.*, 545-549  
in abdominal Hodgkin's disease, *Sept.*, 425  
in cholelithiasis, *Nov.*, 644  
inactivation of chronic infectious arthritis and fibrositis by, *Sept.*, 573-583  
with hepatic insufficiency, treatment, *March*, 1651-1657
- Jejunal ulcer following gastro-enterostomy, *Sept.*, 442
- Joints, diseases of, *Sept.*, 551-583
- Juvenile diabetes, *July*, 273-286
- KARELL diet, *July*, 174
- Kerion of scalp, *Jan.*, 1247, 1248; *March*, 1635

- Ketogenic diet in epilepsy, *July*, 263  
 Kettering hypertherm, *Sept.*, 585  
 Kidney, carcinoma of, roentgen treatment, *Sept.*, 601  
     denervation, for hypertension, *March*, 1359  
     disorders, gastro-intestinal manifestations, *Jan.*, 1262  
     in pregnancy, prevention, *July*, 295-299  
 Koerner's syndrome, *Jan.*, 1052  
 Kolmer's serum in poliomyelitis prophylaxis, *Nov.*, 742; *Jan.*, 1290  
 Kramm's approach to parapharyngeal abscess, *Jan.*, 1159  
 Kraurosis vulvae, *March*, 1446  
 Krueger's pertussis vaccine, *Nov.*, 738, 739; *March*, 1415
- LACERATIONS of cervix, *Sept.*, 348  
 Lambliasis intestinalis in bile, *Nov.*, 680  
 Laryngeal neuralgia, superior, relief of, *Jan.*, 1029  
 Laryngitis, earache in, *Jan.*, 1055  
 Lavage, gastric, for diagnosis of tuberculosis, *Nov.*, 721  
 Lead neuritis, *Nov.*, 953  
     poisoning, abdominal pain in, *March*, 1613  
     in children, convulsions from, *July*, 257  
 Leprous polyneuritis, *Nov.*, 958  
 Leukemia, chronic myelogenous, *Sept.*, 546, 549  
 Leukopenia, pernicious, *July*, 103-122  
 Leukoplakic vulvitis, *March*, 1446  
 Leukorrhea, *Sept.*, 349  
 Lipemia, retinal, *Jan.*, 1233  
 Liver, active principle, *July*, 49, 75  
     storage of, *July*, 57, 58  
     disease in children, pain in, *March*, 1611  
     extract, intra-osseous injection, in pernicious anemia, *July*, 50  
     extrinsic factor, *July*, 49, 51  
     functional tests, *Jan.*, 1165  
     insufficiency, with jaundice, treatment, *March*, 1651-1657  
     therapy in secondary anemias, *July*, 96  
 Liver-stomach mixtures in pernicious anemia, *July*, 49  
 Lobar pneumonia. See *Pneumonia*.  
 Lobectomy for bronchiectasis, *Jan.*, 1175  
 Löwenstein's culture medium in tuberculosis, *Nov.*, 722  
 Lumbago, relief of, *Jan.*, 1033-1038  
 Lumbar puncture in pseudo-uremic convulsions, *July*, 240
- Luminal. See *Phenobarbital*.  
 Lung, abscess of, bronchial obstruction in, *Sept.*, 456, 462  
     complicating pneumonia, *July*, 33, 34  
     carcinoma of, bronchial obstruction in, *Sept.*, 456  
     tuberculosis of. See *Tuberculosis pulmonary*.  
 Lupus erythematosus of scalp, *Jan.*, 1242  
     visceral lesions of, *July*, 333-346  
     miliaris disseminatus faciei, *Sept.*, 617  
 Lyon's test in gallbladder disease, diagnostic value, *Nov.*, 679
- MACULA lutea, *Jan.*, 1200  
 Malarial treatment of rheumatoid arthritis, *March*, 1372  
 Malignant hypertension, *July*, 134  
     tumors, roentgen treatment, *Sept.*, 598-603  
 Mantoux tuberculin test, *Nov.*, 703  
 March foot, *Jan.*, 1075  
 Marmite in pernicious anemia, *July*, 52, 54, 55, 56, 73  
 Marschik's approach to parapharyngeal abscess, *Jan.*, 1158  
 Massage, prostatic, *Jan.*, 1181, 1184  
 Mastoiditis, pain of, relief, *Jan.*, 1044-1047  
 Maxillary sinus infection, pain in, *Jan.*, 1062  
 McBurney's point symptoms in appendicitis, *July*, 190  
 McKhann's placental extract, *March*, 1417  
 Measles, immunization, *Nov.*, 734, 735; *Jan.*, 1287; *March*, 1417  
 Meckel's diverticulum, *Sept.*, 372, 373  
 Mediastinitis, pain in, simulating coronary disease, *Jan.*, 1079  
 Memory impairment, menopausal, *July*, 217  
 Ménière's syndrome, *March*, 1619  
 Meningitis, *Nov.*, 751-769  
 Meningococcus antitoxin, *March*, 1423  
 Menopause, symptoms and treatment, *July*, 205-226; *March*, 1462  
 Menorrhagia, menopausal, *July*, 214  
 Menstruation, delayed, *March*, 1453  
 Mental attitude in inoperable cancer, *July*, 196  
     disorders, puerperal, *Nov.*, 927-941  
 Mercupurin in heart disease, *March*, 1329  
 Mercury polyneuritis, *Nov.*, 955  
 Mersalyl in heart disease, *March*, 1329

- Metabolic disturbances in gallbladder  
 . disease, *Nov.*, 664  
 of pituitary gland, *Nov.*, 832  
 Metropathia hemorrhagica, *March*,  
 1460  
 Metrorrhagia, functional, *Sept.*, 359-  
 364; *March*, 1459  
 Middle ear disease, pain in, *Jan.*, 1041  
 Migraine, relief of, *Jan.*, 1015  
 Miliary tuberculosis, roentgen find-  
 ings, *Nov.*, 712  
 Milk, evaporated, for infants, *Nov.*,  
 787  
 Mitral stenosis, murmurs of, *March*,  
 1514  
 systolic murmur, *March*, 1507  
 Moebius' sign, *Jan.*, 1208  
 Molimina, *March*, 1442  
 Monilia vaginitis, *March*, 1445  
 Moro tuberculin test, *Nov.*, 703  
 Mosher's approach to parapharyngeal  
 abscess, *Jan.*, 1158  
 Motor education, corrective, in birth  
 injuries, etc., *Nov.*, 807-815  
 Mouth care in pneumonia, *July*, 16  
 Mucous colitis, *Jan.*, 1123, 1128  
 membrane of mouth, atrophy of,  
*July*, 59  
 Mumps, *Nov.*, 736  
 immunization, *Jan.*, 1290  
 Murmurs, heart, significance and in-  
 terpretation, *March*, 1505-1518  
 Myoma of small intestines, *Sept.*, 371  
 Myringotomy, *Jan.*, 1042
- Neuralgia, glossopharyngeal, relief of,  
*Jan.*, 1028  
 laryngeal, superior, relief of, *Jan.*,  
 1029  
 occipital, relief of, *Jan.*, 1030  
 Sluder's, relief of, *Jan.*, 1031  
 trigeminal, relief of, *Jan.*, 1017-1028  
 Neurasthenia, traumatic, *Nov.*, 838,  
 839  
 Neurectomy, retrogasserian, for tri-  
 geminal neuralgia, *Jan.*, 1028  
 Neuritis, multiple. See *Polyn neuritis*.  
 optic, in brain abscess, *Jan.*, 1215  
 Neurocirculatory asthenia, *March*,  
 1534-1545  
 Neurological manifestations of per-  
 nicious anemia, with treatment,  
*July*, 79-89  
 Neuropsychoses, menopausal, *July*,  
 216  
 puerperal, *Nov.*, 927-941  
 Neurosis, cardiac, *March*, 1533  
 vertigo due to, *March*, 1620  
 Nervi, spider, *Sept.*, 536  
 Newborn, immunity in, *Nov.*, 733  
 Night blindness in gastro-intestinal  
 affections, *Sept.*, 468, 469  
 Nipple, bleeding, *March*, 1452  
 Nitrites in arterial hypertension,  
*March*, 1347  
 Nitroglycerin in angina pectoris, *Nov.*,  
 882, 883; *Jan.*, 1099  
 Nona, eye symptoms, *Jan.*, 1228  
 Nutritional anemia, *July*, 37-77
- NABOTHIAN cysts, *Sept.*, 349  
 Nail, ringworm of, *March*, 1648  
 Nausea in acute appendicitis, *July*,  
 186, 193  
 in inoperable cancer, treatment,  
*July*, 200  
 Neck, venous hum in, *March*, 1517  
 Neosynthalin as insulin substitute,  
*Nov.*, 803  
 Nephritis, chronic glomerular, com-  
 plicated, *July*, 171-176  
 eye symptoms, *Jan.*, 1235  
 in scarlet fever, treatment, *March*,  
 1396  
 Nephrosis, amyloid, proteosuria in,  
*July*, 177-184  
 complicating chronic glomerular  
 nephritis, *July*, 171  
 Nervous system, syphilis of, fever  
 therapy, *Sept.*, 590  
 vegetative, rôle in climacteric,  
*July*, 210  
 Neufeld reaction for pneumococcus  
 types, Sabin's technic, *July*, 3, 4  
 Neuralgia, dental causes, *Jan.*, 1063
- OBESITY, pituitary, *Nov.*, 827, 832  
 Occipital neuralgia, relief, *Jan.*, 1030  
 Ocular vertigo, *March*, 1619  
 Onychomycosis, *March*, 1648  
 Ophthalmoplegia in epidemic enceph-  
 alitis, *Jan.*, 1228  
 Ophthalmoscopic test, *Jan.*, 1198  
 Optic disk, *Jan.*, 1200  
 neuritis in brain abscess, *Jan.*,  
 1215  
 Organotherapy in pituitary disorders,  
*Nov.*, 818  
 Osteo-arthritis of spine, pain of, sim-  
 ulating angina pectoris, *Jan.*, 1077  
 Otalgia, *Jan.*, 1039  
 Otitis media in scarlet fever, *March*,  
 1391  
 treatment, *March*, 1395  
 pain in, relief, *Jan.*, 1041-1048  
 Otodynia, *Jan.*, 1039  
 Otomycosis, *Jan.*, 1050  
 Ovarian factor in menopause, *July*,  
 205  
 hormones in arterial hypertension,  
*March*, 1353



- Ovarian hormones, urine tests for, *March*, 1440
- Ovarian-pituitary interrelationship, *July*, 206
- Ovulation, *March*, 1447
- Oxygen therapy in congestive heart failure, *March*, 1565
- In pneumonia, *July*, 9-12
- PAIN**, abdominal, clinical significance and relief, *Jan.*, 1113-1129
- in children, *March*, 1603-1615
- severe, following emotional storm, *Sept.*, 399-402
- in acute appendicitis, *July*, 186, 190
- in dental field, *Jan.*, 1057-1066
- in inoperable cancer, control, *July*, 198
- in pelvic lesions of female, relief, *Jan.*, 1122, 1131
- in peptic ulcer, *Jan.*, 1120, 1126
- in pneumonia, treatment, *July*, 13
- in region of heart, *March*, 1533-1545
- relief of, symposium on, *Jan.*, 1013
- shoulder, in gallbladder disease, *Nov.*, 651
- simulating pain of coronary disease, *Jan.*, 1077-1083
- Painful feet, relief of, *Jan.*, 1067-1075
- Palpitation, menopausal, *July*, 216
- Pancreas, disease of, associated with gallbladder disease, *Nov.*, 664
- Pancreatic ferments, *Nov.*, 683
- Paracentesis, abdominal, in congestive failure, *March*, 1570
- of ear drum, *Jan.*, 1042
- Paraldehyde as soporific, *March*, 1599
- Paralysis, birth, corrective motor education, *Nov.*, 807-815
- infantile. See *Poliomyelitis*.
- jake or ginger, *Nov.*, 953
- Parapharyngeal space infections, *Jan.*, 1152
- Parasites in bile, *Nov.*, 680
- Parental serum in measles, *Nov.*, 735
- Paresthesia, menopausal, *July*, 217
- Paronychia, chronic, *March*, 1647
- Paroxysmal tachycardia, *Nov.*, 857-863; *March*, 1325
- Parry's disease, eye symptoms, *Jan.*, 1204
- Patch test in eczema, *July*, 323
- Pediculi, itching due to, *Nov.*, 976
- Pellagra, *July*, 60-62; *March*, 1496
- in gastro-intestinal disease or abnormality, *Sept.*, 468, 470
- vitamin deficiency in, *Sept.*, 478
- Pelvic abscess, gonorrheal, *Nov.*, 921
- inflammatory disease, gonorrheal, *Nov.*, 920
- Pelvic lesions in female, pain of, relief, *Jan.*, 1122, 1131
- sympathectomy, *Jan.*, 1136
- Pelvimetry, prenatal, *March*, 1661
- Peptic ulcer in children, *March*, 1608
- obstructive, diagnosis and management, *March*, 1519-1524
- pain in, *Jan.*, 1120, 1126
- perforation of, pain in, simulating coronary disease, *Jan.*, 1082
- recurrent, reactivated and anastomotic, *Sept.*, 429-452
- Periapical infection, pain in, *Jan.*, 1059
- Pericardial friction rubs, *March*, 1516
- Pericarditis, acute fibrinous, simulating coronary disease, *Jan.*, 1078
- complicating chronic glomerular nephritis, *July*, 171
- constrictive, chronic, *March*, 1336
- uremic, *July*, 238
- Perichondritis, auricular, *Jan.*, 1051
- Peritoneal puncture in pneumococcus peritonitis, *Nov.*, 851, 852
- Peritonitis in children, *March*, 1612
- pneumococcus, *Nov.*, 847, 855
- peritoneal puncture in, *Nov.*, 851, 852
- postoperative, vaccination against, *Sept.*, 620
- Pernicious anemia. See *Anemia, pernicious*.
- leukopenia, *July*, 103-122
- Peroneal sign in tetany, *July*, 255
- Pertussis. See *Whooping cough*.
- Petit mal, *July*, 260
- Petroff's stool examination in tuberculosis, *Nov.*, 721
- Pharyngomaxillary space infections, *Jan.*, 1152
- Phenobarbital in angina pectoris, *Jan.*, 1104
- in epilepsy, *July*, 262; *March*, 1594
- Phrenicectomy for bronchiectasis, *Jan.*, 1175
- Phyone, *Nov.*, 818
- Pick's disease, *March*, 1339
- Picrotoxin poisoning, convulsions in, *July*, 245
- Pigmentation in Addison's disease, *Sept.*, 387
- Pink disease, *Nov.*, 957
- Pitocin, *Nov.*, 819
- Pitressin, *Nov.*, 819
- Pituitary disorders, classification, *Nov.*, 821
- eye symptoms, *Jan.*, 1239
- treatment, *Nov.*, 817-835
- extract, *Nov.*, 818
- in Addison's disease, *Sept.*, 395
- factor in menopause, *July*, 206

- Pituitary hormones, urine tests for, *March*, 1440  
 relationship to hypertension, *March*, 1355  
 solution, *Nov.*, 819
- Pituitary-ovarian interrelationship, *July*, 206
- Pituitrin, *Nov.*, 819
- Placental extracts in measles, *Nov.*, 734; *Jan.*, 1288; *March*, 1417
- Pleural effusion in pulmonary tuberculosis, rapid development, *Nov.*, 907
- Pleurisy, diaphragmatic, abdominal pain in, *Jan.*, 1115  
 fibrinous, pain in, simulating coronary disease, *Jan.*, 1081
- Plummer-Vinson's syndrome, *July*, 71
- Pneumococcus peritonitis, *Nov.*, 847-855  
 types, determining, *July*, 3, 4
- Pneumolysis, perforation of lung following, *Nov.*, 909
- Pneumonia, abdominal pain in, *Jan.*, 1115; *March*, 1613  
 artificial pneumothorax in, *July* 19-27  
 digitalization in, *July*, 14  
 nursing care and diet in, *July*, 15-18  
 oxygen therapy, *July*, 9-12  
 pain in, simulating coronary disease, *Jan.*, 1081  
 specific therapy, *July*, 3-9  
 surgical complications, *July*, 29-35  
 symptomatic treatment, *July*, 12-14
- Pneumothorax, artificial, air embolism during, *Nov.*, 908  
 in hemoptysis of pulmonary tuberculosis, *Nov.*, 904  
 in lobar pneumonia, *July*, 19-27  
 spontaneous, in pulmonary tuberculosis, treatment, *Nov.*, 904-907  
 pain in, simulating coronary disease, *Jan.*, 1080
- Poliomyelitis, acute anterior, immunization, *Jan.*, 1290  
 recent developments, *Nov.*, 740-744
- Politzer bag ear inflation, *Jan.*, 1042
- Pollen hay fever, curability of, *March*, 1483, 1547-1562
- Polyneuritis, *July*, 68; *Nov.*, 943  
 treatment, *Nov.*, 943-958  
 vitamin deficiency in, *Sept.*, 478, 481
- Post cautery in gonorrhea of cervix, *Nov.*, 915
- Postoperative arthritis, acute, identification of, *Sept.*, 560-566  
 prevention and treatment, *Sept.*, 566-573
- Postoperative gas pains, *Jan.*, 1125
- Postural hypotension, *Nov.*, 868
- Postvaccinal encephalitis, *Jan.*, 1280
- Potassium iodide in angina pectoris, *Jan.*, 1104  
 thiocyanate in arterial hypertension, *March*, 1352
- Pregnancy, anemia of, *July*, 38, 65  
 heart disease in, management, *Nov.*, 893-899  
 kidney disorders in, prevention, *July*, 295-299  
 polyneuritis, *Nov.*, 953  
 tests, *March*, 1452
- Premenstrual feelings, *March*, 1442
- Prenatal care in private practice, *March*, 1659-1671
- Preoperative vaccination against peritonitis, *Sept.*, 620, 626
- Prize fighter ear, *Jan.*, 1053
- Proctitis, gonorrheal, *Nov.*, 921
- Progestin, *March*, 1463  
 in amenorrhea, *March*, 1454  
 in dysmenorrhea, *March*, 1457
- Prolactin, *Nov.*, 819
- Prolan, *Nov.*, 818; *March*, 1462  
 in functional bleeding, *March*, 1460, 1461  
 in urine, test, *March*, 1440
- Prolution in functional metrorrhagia in young women, *Sept.*, 361
- Prostate gland, rectal palpation, *Jan.*, 1181
- Prostatic massage, *Jan.*, 1181, 1184
- Prostatitis, *Jan.*, 1181
- Protein sensitization test, *March*, 1471
- Proteosuria in amyloid nephrosis, *July*, 177-184
- Pruritus, *Nov.*, 971-980  
 in Hodgkin's disease, *Sept.*, 426; *Nov.*, 967-970  
 treatment, *Nov.*, 980-987  
 vulvae, *March*, 1445
- Pseudonarcotism at menopause, *July*, 218
- Pseudo-uremia, *July*, 236, 238  
 convulsions of, *July*, 238-241
- Psychic effect of abdominal trauma, *Nov.*, 837-845
- Psychoanalysis in puerperal psychoses, *Nov.*, 941
- Psychoses, menopausal, *July*, 216, 218  
 puerperal, *Nov.*, 927-941
- Puerperal polyneuritis, *Nov.*, 957  
 psychoses, *Nov.*, 927-941
- Pulmonary. See also *Lungs*.  
 embolism simulating coronary disease, *Jan.*, 1079  
 regurgitation, murmur in, *March*, 1515
- Pulpitis, pain in, *Jan.*, 1057

- Pupil tests, *Jan.*, 1196  
 Purin derivatives in congestive heart failure, *March*, 1569  
     in nephritis with vascular and cardiac complications, *July*, 175  
 Purpura hemorrhagica in scarlet fever, treatment, *March*, 1398  
     in children, abdominal pain in, *March*, 1612  
 Pyemia following tonsillar infections, treatment, *Jan.*, 1151  
 Pyloric stenosis, hypertrophic, congenital, *March*, 1604  
 Pyloroplasty for peptic ulcer, recurrence after, *Sept.*, 440  
 Pyoderms, staphylococcus toxoid in, *March*, 1431  
 Pyrexia in children, convulsions due to, *July*, 252  
  
 QUINIDINE therapy in heart disease, *March*, 1322  
 Quinine in paroxysmal tachycardia, *Nov.*, 861  
     in pneumonia, *July*, 6  
  
 RABIES, immunization, *Jan.*, 1290  
 Radium treatment of functional metrorrhagia, *Sept.*, 363  
 Raynaud's disease, treatment, *July*, 148  
 Rectum, gonorrhea of, *Nov.*, 921  
 Renal colic, *Jan.*, 1119, 1124  
 Resistance to infections, vitamins and, *Sept.*, 471  
 Respirator in poliomyelitis, *Nov.*, 743  
 Respiratory tract infections, abdominal pain in, *March*, 1613  
 Rest in angina pectoris, *Jan.*, 1097  
     in congestive heart failure, *March*, 1563  
     in hypertension, *July*, 143  
     in pneumonia, *July*, 15  
     in tuberculosis, *July*, 228, 230  
 Reticulocyte count in pernicious anemia, *July*, 40  
 Retinal hemorrhages in diabetes, *Jan.*, 1234  
     lipemia, *Jan.*, 1233  
     vessels, examination, *Jan.*, 1201  
 Retinitis, albuminuric, *Jan.*, 1236  
     arteriosclerotic, *Jan.*, 1210  
     diabetic, *Jan.*, 1232  
 Rheumatic fever, abdominal pain in, *March*, 1613  
 Rheumatism, gonorrheal, *Sept.*, 551  
 Rheumatoid arthritis, treatment, *March*, 1370-1375  
  
 Rhinitis, purulent, in scarlet fever, treatment, *March*, 1395  
     vasomotor, *March*, 1468, 1547  
 Rhizotomy for essential hypertension, *Sept.*, 523  
 Ribs, fracture of, pain in, simulating coronary disease, *Jan.*, 1081  
 Rickets, dietetic factor, *Jan.*, 1291-1304  
     tetany due to, *July*, 255  
     vitamin deficiency in, *Sept.*, 478, 483  
 Ringworm of beard, *March*, 1638  
     of nail, *March*, 1648  
     of scalp, *Jan.*, 1241-1250; *March*, 1635  
 Roentgen diagnosis of tuberculosis in children, *Nov.*, 706-721  
     epilation of scalp, *Jan.*, 1246; *March*, 1637, 1639  
     treatment of inflammatory and malignant conditions, *Sept.*, 597-603  
     of pruritus, *Nov.*, 983  
     of syringomyelia, *March*, 1578  
 Roseola infantum, abdominal pain in, *March*, 1613  
 Rowe's elimination diets, *March*, 1490  
 Rupture of ear drum, traumatic, *Jan.*, 1054  
 Rush method of desensitization, *March*, 1483  
  
 SABIN's technic for Neufeld reaction for pneumococcus types, *July*, 3, 4  
 Salpingitis, gonorrheal, *Nov.*, 919, 920  
     fever therapy, *Sept.*, 588, 590  
 Salt therapy in Addison's disease, *Sept.*, 391; *Nov.*, 959-965  
 Salyrgan in congestive heart failure, *March*, 1569  
     in heart disease, *March*, 1326  
 Sarcoma of small intestine, *Sept.*, 370  
 Sauer's pertussis vaccine, *Nov.*, 738; *Jan.*, 1288; *March*, 1413  
 Scalp, ringworm and related lesions of, *Jan.*, 1241-1250; *March*, 1635  
     x-ray epilation, *Jan.*, 1246; *March*, 1637, 1639  
 Scarlet fever, *Nov.*, 739  
     complications, *March*, 1391  
         treatment, *March*, 1395-1399  
     Dick test, *Jan.*, 1285  
     immunization, *Jan.*, 1285  
     treatment, *March*, 1389-1395  
 Schick test, *Jan.*, 1282  
 School problems in diabetes, *July*, 282  
 Sciatica, relief of, *Jan.*, 1033-1038  
 Scratch test in hay fever, *March*, 1472  
 Scurvy, *March*, 1493  
     vitamins and, *Sept.*, 478

- Sea sickness, *March*, 1619
- Sedimentation test in tuberculosis in children, *Nov.*, 724
- Sensitization tests in hay fever, *March*, 1471, 1553
- Sepsis following tonsillar infections, treatment, *Jan.*, 1151
- Septic sore throat, *Jan.*, 1143
- Serum prophylaxis of poliomyelitis, *Nov.*, 742; *Jan.*, 1290
- reaction in meningitis, *Nov.*, 766
- sickness from scarlet fever anti-toxin, *March*, 1393
- treatment of diphtheria, *March*, 1401
- of meningitis, *Nov.*, 760; *March*, 1423
- of pneumonia, *July*, 3-6
- of scarlet fever, *March*, 1389
- Serums, recent advances, *March*, 1409-1434
- Sex determination, *March*, 1448
- Sexual desire and hypertension, *July*, 146
- Shoulder pain in gallbladder disease, *Nov.*, 651
- Simmond's disease, *Nov.*, 825
- Sinus, maxillary, disease of, pain in, *Jan.*, 1062
- Sinusitis in scarlet fever, treatment, *March*, 1396
- Sistomensin in functional metrorrhagia in young women, *Sept.*, 361
- Skene's glands, gonorrheal inflammation, *Nov.*, 922
- Skin, diseases of, *March*, 1627-1649
- infections, staphylococcus toxoid in, *March*, 1431
- tests in hay fever, *March*, 1472, 1553
- tuberculosis of, *Sept.*, 611-618
- tumors of, roentgen therapy, *Sept.*, 599
- Skull fractures, eye symptoms, *Jan.*, 1238
- Sleeping sickness, eye symptoms, *Jan.*, 1228
- Sluder's neuralgia, relief of, *Jan.*, 1031
- Smallpox, vaccination, *Jan.*, 1277
- Snellen test types, *Jan.*, 1190
- Soldier's heart, *March*, 1534
- Soporifics, use of, *March*, 1598
- Sore throat, septic, *Jan.*, 1143
- Spasmiophilia, *July*, 254
- Spastic colon in children, *March*, 1608
- Speech disturbances in birth injuries, *Nov.*, 810, 812
- Spider nevi, *Sept.*, 536
- Spinal disease, abdominal pain in, *March*, 1614
- fluid, examinations in meningitis, *Nov.*, 758
- Spinal nerve root resection for hypertension, *March*, 1359
- Spine, osteo-arthritis of, simulating angina pectoris, *Jan.*, 1077
- Splanchnic nerve section for hypertension, *March*, 1356
- Splenectomy for pernicious anemia, *July*, 44
- value of, in jaundice from atypical blood dyscrasias, *Sept.*, 550
- Sporotrichosis of skin, *March*, 1647
- Sprue, *July*, 62-64; *March*, 1496
- Staphylococcus antitoxin, *March*, 1426
- toxin, *March*, 1426
- toxoid, *March*, 1426
- Stasis-edema in thrombophlebitis, *Sept.*, 542
- in varicose veins, *Sept.*, 538
- Status epilepticus, *July*, 261
- Steatorrhea, idiopathic, *July*, 66; *March*, 1688
- Stellwag's sign, *Jan.*, 1208
- Sterility in female, *March*, 1449
- Stokes-Adams attacks, *July*, 243; *March*, 1625
- Stomach, carcinoma of, inoperable, *July*, 195
- in development of pernicious anemia, *July*, 40
- secretory, motor and sensory disturbances in gallbladder disease, *Nov.*, 660-662
- Stools, Petroff's examination in tuberculosis, *Nov.*, 721
- Streptococcic sore throat, *Jan.*, 1143
- Stridor, significance in tracheal and bronchial obstruction, *Sept.*, 454
- Strychnine poisoning, convulsions in, *July*, 244, 256
- Subperichondrial abscess, *Jan.*, 1051
- Suburethral abscess, gonorrheal, *Nov.*, 922
- Sulphur treatment of rheumatoid arthritis, *March*, 1374
- Suprarenal glands, denervation for hypertension, *March*, 1358
- in Addison's disease, *Sept.*, 384, 386, 390
- origin of hypertension, *March*, 1355
- Suprarenalectomy for hypertension, *March*, 1358
- Sympathectomy for hypertension, *March*, 1356
- pelvic, *Jan.*, 1136
- Syncope, significance and treatment, *March*, 1617, 1621-1626
- Synthelin as insulin substitute, *Nov.*, 803
- Syphilis, eye symptoms, *Jan.*, 1239
- of nervous system, fever therapy, *Sept.*, 590

- Syngomyelia, diagnosis and treatment, *March*, 1571-1582  
 Systolic murmur, *March*, 1507
- TABES, eye symptoms, *Jan.*, 1238  
 Tachycardia, paroxysmal, *Nov.*, 857-863; *March*, 1325  
 Teeth, unerupted and impacted, pain due to, *Jan.*, 1062  
 Telangiectases, *Sept.*, 536  
 Temporomandibular joint diseases, pain in, *Jan.*, 1065  
 Tension of eye, testing, *Jan.*, 1194  
 Test types, visual, *Jan.*, 1190  
 Testis, tumors of, roentgen treatment, *Sept.*, 599  
 Tetanus, immunization, *Jan.*, 1284; *March*, 1420-1423  
   neonatorum, *July*, 251  
 Tetany, *July*, 241-243  
   infantile, *July*, 254  
 Thallium acetate in tinea, *March*, 1638  
   neuritis, *Nov.*, 955  
 Theobromine in angina pectoris, *Jan.*, 1101  
 Theophylline in angina pectoris, *Jan.*, 1101  
 Theophylline - ethylene - diamine in heart disease, *March*, 1321  
 Thiocyanate in arterial hypertension, *March*, 1351  
 Throat, sore, septic, *Jan.*, 1143  
 Thrombophlebitis, *Sept.*, 539-543  
 Thrombosis, coronary, angina pectoris and, differentiation, *Jan.*, 1085  
   treatment, *Nov.*, 873-880, 887  
   of aorta and its larger branches, *July*, 159-170  
 Thyroid gland, carcinoma of, roentgen therapy, *Sept.*, 600  
   diseases, gastro-intestinal manifestations, *Jan.*, 1258  
   treatment, *March*, 1377-1387  
 Thyroidectomy for angina pectoris, *Jan.*, 1105; *March*, 1333  
   for congestive heart failure, *March*, 1570  
 Tic douloureux, relief of, *Jan.*, 1017  
 Tinea barbae, *March*, 1638  
   capitis, *March*, 1635, 1636  
   circinata, *March*, 1639  
   favosa, *March*, 1636  
   sycosis, *March*, 1638  
   unguim, *March*, 1648  
   versicolor, *March*, 1645  
 Tinnitus, menopausal, *July*, 218  
 Tissue extracts in angina pectoris, *Jan.*, 1103  
   in arterial hypertension, *March*, 1348
- Tobacco, use of, in angina pectoris, *Nov.*, 883; *Jan.*, 1099  
 Tongue, black, *July*, 59  
   burning, *Jan.*, 1065  
 Tonsillar infections, sepsis and pyemia after, treatment, *Jan.*, 1151  
 Toothache, *Jan.*, 1057  
   ear pain in, *Jan.*, 1055  
 Toxoid, diphtheria, *Nov.*, 736; *Jan.*, 1281  
   staphylococcus, *March*, 1426  
   tetanus, *Jan.*, 1285; *March*, 1420  
 Trachea, obstruction of, clinical and bronchoscopic findings, *Sept.*, 453-462  
 Transfusions, blood, from convalescents in scarlet fever, *March*, 1394  
   in functional metrorrhagia, *Sept.*, 362  
   in inoperable cancer, *July*, 202  
   in measles, *Jan.*, 1288  
   in secondary anemias, *July*, 99  
 Trendelenburg's test in varicose veins, *Sept.*, 536  
 Trichomoniasis, vaginal, *March*, 1443  
 Trichophytide, *March*, 1644  
 Trigeminal neuralgia, relief of, *Jan.*, 1017-1028  
 Tropical macrocytic anemia, *July*, 66  
 Trousseau's sign in tetany, *July*, 242  
 Tuberculin reaction, *Nov.*, 702-706  
 Tuberculosis, cutaneous, hematogenous type, *Sept.*, 611-618  
   miliary, roentgen findings, *Nov.*, 712  
   of small intestine, *Sept.*, 379  
   of suprarenal glands in Addison's disease, *Sept.*, 384  
   pulmonary, abdominal pain in, *Jan.*, 1116  
   bronchial obstruction in, *Sept.*, 456  
   crises in, management, *Nov.*, 901-909  
   gastro-intestinal manifestations, *Jan.*, 1258  
   home treatment, *July*, 227-231  
   in children, diagnosis, *Nov.*, 701-729  
 Tuberculous bronchopneumonia in children, *Nov.*, 717  
   hilar nodes, *Nov.*, 711  
   meningitis, *Nov.*, 758, 759  
   peritonitis in children, *March*, 1612  
 Tumors, abdominal, in children, pain in, *March*, 1611  
   gynecological, of endocrine significance, *March*, 1446  
   malignant, roentgen treatment, *Sept.*, 598-603  
   of brain. See *Brain, tumors of.*

- mors of small intestine, *Sept.*, 366,  
 370  
 of trachea, obstructive, *Sept.*, 454  
 pituitary, *Nov.*, 832  
 phoid fever, immunization, *Jan.*,  
 1284  
 LCER, gastrojejunal, following gas-  
 tro-enterostomy, *Sept.*, 442  
 of ileum, *Sept.*, 380  
 peptic. See *Peptic ulcer*.  
 varicose, *Sept.*, 539  
 lceration, uremic, *July*, 238  
 lcerative colitis, chronic, manage-  
 ment, *Sept.*, 403-407  
     two carcinomas complicating,  
     *Sept.*, 408-410  
     idiopathic, in children, *March*,  
     1673-1683  
 enterocolitis, regional, *Sept.*, 411-  
 422  
 Ultraviolet treatment of pruritus,  
*Nov.*, 983  
     of secondary anemias, *July*, 98  
 Unconsciousness in heart block, *July*,  
 243  
 Urea frost, *July*, 237  
 Uremia, *July*, 236-241  
     convulsions in, *July*, 236  
     in children, *July*, 258  
 Uremic poisoning, treatment, *Jan.*,  
 1270  
 Urethra, female, gonorrheal infection,  
*Nov.*, 912, 922  
     stricture, *Nov.*, 925  
     milking of, *Nov.*, 913  
 Urethral caruncle, *Nov.*, 923  
 Urethritis, gonococcal, fever therapy,  
*Sept.*, 588  
 Urinary incontinence in children, *July*,  
 287-294  
     tract diseases, gastro-intestinal man-  
     ifestations, *Jan.*, 1253, 1255  
     in children, abdominal pain in,  
     *March*, 1611  
 Urine examination in pregnancy,  
*March*, 1663  
     tests for pituitary and ovarian hor-  
     mones, *March*, 1440  
 Uterine bleeding, functional, *Sept.*,  
 364; *March*, 1459  
     menopausal, *July*, 214  
     cervix. See *Cervix uteri*.  
 Uterus, dilatation of, *March*, 1458  
     measurement of, *March*, 1441  
 Vaccine, poliomyelitis, *Nov.*, 742; *Jan.*,  
 1290  
     prophylaxis of colds, *Nov.*, 749;  
     *March*, 1503  
     rabies, *Jan.*, 1290  
     Sauer's pertussis, *Nov.*, 738; *Jan.*,  
     1288; *March*, 1413  
     smallpox, *Jan.*, 1277  
     treatment of hay fever and asthma,  
     *March*, 1487  
     of pneumonia, *July*, 6  
     of rheumatoid arthritis, *March*,  
     1373  
     typhoid fever, *Jan.*, 1284  
 Vaccines, recent advances, *March*,  
 1409-1434  
 Vaginal complications in gonorrhea,  
*Nov.*, 919  
     inflammations and discharges,  
     *March*, 1443  
 Valsalva ear inflation, *Jan.*, 1042  
 Van den Bergh reaction, *Jan.*, 1166  
 Varicose ulcers, *Sept.*, 539  
     veins, *Sept.*, 535-538  
 Vascular crises in hypertension, man-  
 agement, *July*, 133, 143  
 Vasomotor rhinitis, *March*, 1468, 1547  
 Vasovagal syncope, *March*, 1622  
 Vegex in pernicious anemia, *July*, 56,  
 73, 74  
 Veins, diseases of, *Sept.*, 535-543  
 Venesection in congestive heart fail-  
 ure, *March*, 1570  
     in pseudo-uremic convulsions, *July*,  
     240  
 Venous hum in neck, *March*, 1517  
     pressure, *Jan.*, 1273-1276  
 Vertigo e vesica fellea laesa, *Nov.*,  
 653  
     in gallbladder disease, *Nov.*, 652  
     menopausal, *July*, 218  
     significance and treatment, *March*,  
     1617-1621  
 Viosterol in hay fever and asthma,  
*March*, 1488  
 Virus diseases, *Nov.*, 732  
 Visceral lesions of lupus erythemato-  
 sus, *July*, 333-346  
 Visual tests, *Jan.*, 1190, 1193  
 Vitamin B and pernicious anemia,  
*July*, 51, 74  
     factor in colds, *Nov.*, 748  
     therapy in secondary anemias, *July*,  
     97  
 Vitamins, *Sept.*, 463-476; *March*, 1494  
     chemical nature, *Sept.*, 477-485  
 Volvulus, *Sept.*, 378  
 Vomiting in acute appendicitis, *July*,  
 186, 193  
     in inoperable cancer, treatment,  
     *July*, 200

- |   |  |
|---|--|
| Von Graefe's sign, <i>Jan.</i> , 1207<br>Vulva, itching, <i>March</i> , 1445, 1446<br>Vulvovaginal gland, gonorrhea of, <i>Nov.</i> , 919<br>Vulvovaginitis, gonorrheal, in children, <i>March</i> , 1445<br><br>WEAKNESS in inoperable cancer, treatment, <i>July</i> , 201<br>Westphal's sign, <i>Nov.</i> , 652<br>Whooping cough, <i>Nov.</i> , 732 | Whooping cough, vaccine prophylaxis and treatment, <i>Nov.</i> , 738, 739; <i>Jan.</i> , 1288; <i>March</i> , 1409-1417<br><br>XEROPHTHALMIA and vitamin deficiency, <i>Sept.</i> , 478<br><br>YEASTS, autolyzed, in pernicious anemia, effects, <i>July</i> , 51, 57<br><br>ZOSTER auriculæ, Hunt's, <i>Jan.</i> , 1052 |
|---|--|







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# CONTENTS

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	PAGE
SYMPOSIUM ON THE MEDICAL ASPECTS OF THYROID DISEASE.....	1713
Prevention and Treatment of Endemic Goiter and Its Complications.....	1715
By Drs. GEORGE CRILE and GEORGE CRILE, JR.	
The Management of Complicating Factors in Hyperthyroidism.....	1725
By DR. A. CARLTON ERNSTENE	
Atypical Hyperthyroidism.....	1733
By DR. E. PERRY McCULLAGH	
Diagnosis and Treatment of Hypothyroidism.....	1743
By DR. C. L. HARTSOCK	
Clinical Problems Associated with Malignancy of the Thyroid Gland.....	1755
By Drs. ROBERT S. DINSMORE and JAMES H. YANT	
The Diseases of the Thyroid Gland and Their Response to Roentgen and Radium Therapy.....	1765
By DR. U. V. PORTMANN	
Preoperative and Postoperative Treatment of the Patient with Hyperthyroidism.....	1783
By DR. GEORGE CRILE, JR.	
Diagnosis and Treatment of Nocturnal Indigestion.....	1797
By DR. C. L. HARTSOCK	
The Treatment of Splanchnoptosis.....	1807
Intestinal Toxemia.....	1819
By DR. JOHN TUCKER	
Diagnosis of Cancer of the Colon.....	1831
By DR. THOMAS E. JONES	
Diet in the Treatment of Arthritis.....	1837
By DR. RUSSELL L. HADEN	
The Treatment of Emaciation.....	1849
By DR. R. H. McDONALD	
Emergency Management in the Crises of Heart Disease.....	1857
By DR. A. CARLTON ERNSTENE	
Diagnosis and Treatment of Essential Hypertension.....	1865
By DR. R. H. McDONALD	
Remarks on a Few Common Skin Eruptions Seen Frequently During the Summer Months.....	1875
Pruritus Vulvae.....	1893
By DR. E. W. NETHERTON	
The Treatment of Hay Fever in General Practice.....	1915
By Drs. I. M. HINNANT and FARRIS D. EVANS	
The Influence of Food Allergy on Mild and Severe Cyclic Vomiting.....	1931
By Drs. I. M. HINNANT and L. J. HALPIN	
The Treatment of Burns.....	1941
By DR. GEORGE CRILE, JR.	
Endocrine Therapy of Benign Prostatic Hypertrophy.....	1949
By Drs. WILLIAM E. LOWER and D. ROY McCULLAGH	
The Symptoms, Diagnosis and Treatment of Cystitis.....	1959
By DR. C. C. HIGGINS	
The Diagnosis of Blood Dyscrasias in Children.....	1967
The Transfusion of Blood in General Medical Practice.....	1977
By DR. RUSSELL L. HADEN	
Constitutional Psychopathic Personalities: Their Recognition, Diagnosis and Management.....	1985
By DR. LOUIS J. KARNOSHI	
The Diagnosis and Newer Treatment of Gonorrheal Vulvovaginitis in Children.....	1999
By DR. WILLIAM J. ENGEL	
Treatment of Chronic Hypoglycemia.....	2005
By DR. E. PERRY McCULLAGH	
Index to Volume 19.....	2021

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**SYMPOSIUM ON THE MEDICAL ASPECTS OF  
THYROID DISEASE**

The following clinics are included in this Symposium:

George Crile and George Crile, Jr.: PREVENTION AND TREATMENT OF ENDEMIC  
GOITER AND ITS COMPLICATIONS.

A. Carlton Ernstene: THE MANAGEMENT OF COMPLICATING FACTORS IN HYPER-  
THYROIDISM.

E. Perry McCullagh: ATYPICAL HYPERTHYROIDISM.

C. L. Hartsock: DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM.

Robert S. Dinsmore and James H. Yant: CLINICAL PROBLEMS ASSOCIATED WITH  
MALIGNANCY OF THE THYROID GLAND.

U. V. Portman: THE DISEASES OF THE THYROID GLAND AND THEIR RESPONSE  
TO ROENTGEN AND RADIUM THERAPY.

George Crile, Jr.: PRE- AND POSTOPERATIVE TREATMENT OF THE PATIENT WITH  
HYPERTHYROIDISM.



## PREVENTION AND TREATMENT OF ENDEMIC GOITER AND ITS COMPLICATIONS

GEORGE CRILE AND GEORGE CRILE, JR.

IN certain parts of the country, such as in the region of the Great Lakes, endemic goiter is prevalent. The iodine in this region has been washed from the soil and has flowed from the lakes to the sea. Therefore, the iodine intake of the average person is very low, and although it usually is sufficient for ordinary requirements, it may at times of particular endocrine activity fall below the level of physiological necessity, and result in a relative iodine deficiency.

Thyroxin, the active agent of thyroid secretion, is 65 per cent iodine. When a deficiency of iodine in the diet is present, the thyroid gland finds itself in the position of a factory attempting to maintain its output during a famine of raw material. The gland rapidly utilizes its store of iodine-containing colloid and undergoes hypertrophy and hyperplasia in an attempt to keep up its production of thyroxin. Although subsequent involution to the colloid phase occurs, these changes produce permanent alterations of thyroid histology, lay the foundation for endemic goiter and often result in the development of adenomata with their attendant complications of hyperthyroidism, growth to deforming size, and development of malignant change.

The times of greatest physiological stress so far as the thyroid gland is concerned are (1) during pregnancy and (2) during puberty and adolescence. To a lesser degree, infancy and childhood are characterized by excessive metabolic demands, but puberty and pregnancy deserve particular consideration.



## IODINE DEFICIENCY IN PREGNANCY

Since early times, the enlargement of the thyroid gland associated with pregnancy has been noted. The basal metabolic rate in normal pregnancy may be elevated, and this is not surprising in view of the known activities of the glands of internal secretion at this time.

The appearance of or enlargement of a goiter at the time of pregnancy is a common finding in the history of patients in regions where the iodine content of the soil and water is low and where endemic goiter is prevalent. One may readily understand this change when one realizes that pregnancy is a period of increased thyroid activity and hence of increased physiological demand for iodine. For these reasons, we believe that every pregnant woman, who lives in regions where endemic goiter is prevalent, should have the benefit of prophylactic maintenance doses of iodine.

Iodized salt, in the early years of its use, fell into some disrepute because of the relatively enormous and unphysiological quantities of iodine it contained. It was thought that in some instances these larger doses of iodine had induced hyperthyroidism in previously inactive adenomata. But at the present time, the common brands of iodized salt contain only 1 part per 5000 of iodine, and the daily intake of iodine by a person who lives in a region of endemic goiter and uses iodized salt is no greater than that of a person who lives by the sea and uses uniodized salt.

A 25 per cent solution of potassium iodide in doses of one minim once a week is the cheapest form in which prophylactic doses of iodine may be prescribed. If tablet form is preferred, one iodostarin tablet is taken each Sunday morning and this will insure an intake of 10 mg. of iodine a week. Since the total requirements for a year are certainly not over 100 mg., an ample supply is thus afforded. By thus supplying the physiological demands of pregnancy, not only is goiter in the mother prevented, but congenital goiter and cretinism in the child may be avoided.

## IODINE DEFICIENCY IN PUBERTY AND ADOLESCENCE

Although an adequate intake of iodine should be afforded the growing child, it is doubly important that the adolescent child should have prophylactic doses of iodine. At puberty, the thyroid shares in the general endocrine awakening of the child; it enlarges, becomes more vascular, and if any iodine deficiency exists, the gland may undergo a rapid hypertrophy and hyperplasia. In the presence of such an iodine deficiency, the superior thyroid arteries pulsate forcibly, and the gland may become so vascular that a bruit can be detected, although the basal metabolic rate is normal and there is no clinical evidence of hyperthyroidism. The involution of such a gland to the colloid phase results in the typical adolescent goiter. The prophylaxis of such changes consists merely in the administration of iodine in the same form and doses as those prescribed for iodine deficiency during pregnancy. The treatment of the fully developed adolescent goiter is a separate problem which will be discussed later in conjunction with the other complications that may follow iodine deficiency.

## DIAGNOSIS AND TREATMENT OF CRETINISM AND CHILDHOOD HYPOTHYROIDISM

True cretinism is a rare condition in this country, but textbooks have made everyone familiar with the clinical picture of the mentally and physically retarded, pot-bellied, big-tongued cretin. Childhood hypothyroidism on the other hand, presents a diagnostic problem of considerable magnitude in that it must be differentiated from the pituitary dyscrasias, the skeletal maldevelopments (chondrodystrophies, etc.), and mental retardations as well as from dwarfism secondary to infectious or nutritional disorders.

The relationship between hypothyroidism in childhood and iodine deficiency is uncertain, but its treatment, like the treatment of cretinism, is by the use of desiccated thyroid and not by iodine. The basal metabolic rate is not a satisfactory diagnostic criterion in children, and of more clinical significance than the finding of a low metabolism is the presence of retarded

dentition and delayed epiphyseal development. The blood cholesterol is quite consistently high in the presence of hypothyroidism in childhood and is a most dependable diagnostic aid. Unfortunately, the determination of the blood iodine is of more value in the diagnosis of hyperthyroidism than of hypothyroidism.

The daily doses which are necessary to correct childhood hypothyroidism vary from 1 to 3 grains of U.S.P. thyroid and this should be adjusted in accordance with the clinical response of the patient and the response of the blood cholesterol. It is usually well to begin with small doses which may be increased gradually.

#### ADOLESCENT GOITER

Adolescent goiter can always be prevented, but rarely can it be cured by medical treatment. In some cases, if the changes have been present for a relatively short time, if the patient is in the early teens, and if adequate doses of iodine (such as a 25 per cent solution of potassium iodide in one minimum dose given twice a week or 2 tablets of iodostarin each week) are given and are supplemented by thyroid in doses up to  $\frac{1}{2}$  grain daily when the basal metabolic rate is normal, or in quantities sufficient to correct any hypometabolism that may be present, a gradual diminution in the size of the gland may be noted. In older children, however, and particularly in those more than eighteen years of age, little regression can be expected and the most we can hope for is prevention of further enlargement. There is no reason to consider the surgical removal of a diffuse, adolescent goiter unless it is extremely large and the patient desires its removal for cosmetic reasons.

#### THE DIFFUSE ADENOMATOUS GOITER

In the goiter regions of Switzerland, Wegelin's autopsy studies<sup>1</sup> have shown that (1) in the younger groups, nearly 100 per cent of the thyroid glands which were examined showed the presence of diffuse goiters; (2) as age advanced, an increasing percentage of nodular goiters were found; and (3) in the oldest groups, 100 per cent of the goiters were of

the nodular type. These figures show that the development of adenomata in a goitrous gland is nearly certain to occur if the patient lives long enough for these changes to take place.

We know that the serious complications of goiter are (1) hyperthyroidism, (2) intrathoracic growth, (3) growth to excessive size, and (4) the development of malignant tumors. More than 90 per cent of all malignant epithelial tumors of the thyroid have their origin in preexisting adenomata (Graham).<sup>2</sup> Practically all intrathoracic goiters are adenomata which have grown downward into the thorax. Hyperthyroidism, aside from true Graves' disease, is nearly certain to be associated with an adenomatous type of gland. What steps are we justified in taking to avoid the development of these serious complications? In short, should the routine removal of all nodular goiters be recommended?

It is quite obvious that the removal of all nodular goiters would be utterly impractical. In the first place, the incidence of adenomatous goiter is extremely high and in some regions the majority of the population may be affected. In the second place, the type of adenomatosis which is present in these cases appears, as Reinhoff's<sup>3</sup> studies have indicated, to be a physiological process of degeneration and regeneration and involves the entire gland. Therefore, even after a subtotal thyroidectomy had been performed, a certain amount of adenomatous tissue would remain. And lastly, experience has shown us that malignant change is a relatively rare finding in the diffuse adenomatous gland. Hyperthyroidism, moreover, can be treated safely and cured surgically after it has appeared, and a substernal goiter can likewise be removed with safety after its symptoms bring the patient to the physician. In this type of gland, therefore, prophylactic thyroidectomy is not recommended and our policy is that of careful observation.

The indications for prompt thyroidectomy are (1) enlargement of an adenoma in a patient over thirty-five years of age; (2) the development of hyperthyroidism; (3) pressure symptoms denoting intrathoracic extension or tracheal compression; and (4) for cosmetic reasons at the patient's request. The

removal of a large goiter is also indicated in the presence of symptoms such as fatigue, palpitation and dyspnea, which are perhaps the result of a combination of psychic and mechanical factors, as well as of the presence of a large, vascular bed which places excessive strain on the myocardium.

### THE DISCRETE ADENOMA

A different problem is presented by the finding of a firm, circumscribed, discrete adenoma, particularly in a patient beyond middle age. Even if there is no evidence of hyperthyroidism, even if the adenoma is of relatively small size, and even if there had been no recent growth, its removal should be advised.

The discrete adenoma has certain clinical and pathological qualities of neoplasia which render its management a different problem from that of the diffuse adenomatous gland, and it is in this type of tumor that we believe malignant change is most commonly seen. At least 2 per cent of such adenomata are found by the pathologist to be malignant despite the fact that the diagnosis is not suspected before operation. For this reason, we believe discrete adenomata should be removed before the patient reaches the age of thirty-five years. The following case illustrates this point:

The patient was a married woman aged forty-two years who was first seen at the Cleveland Clinic in September, 1922, complaining of goiter. Physical examination showed a small nodular enlargement of the thyroid gland. Dr. Crile, Sr., who saw the patient in consultation, made a diagnosis of fetal adenoma of the thyroid and recommended thyroidectomy. The patient refused operation and was not seen again until nearly three years after the first examination.

In 1925 she returned to the clinic complaining of enlargement of the thyroid and of pain in the left side of the neck which radiated upward behind the ear. Examination showed a large, hard, fixed goiter, and a diagnosis of malignant adenoma of the thyroid was made. Complete removal of the tumor was impossible. x-Ray therapy was given and temporary improvement followed, but the tumor recurred. Over a five-year period, the recurrences were held in control by x-ray therapy, but finally in 1930, the tumor lost its radiosensitivity and a decompression operation for relief of dyspnea was performed. The pathologic report of the tissues removed was malignant adenoma. The patient died in December, 1930 as a result of tracheal invasion by the tumor.

Had operation been performed when first advised, it is highly probable that the adenoma had not as yet become malignant and that a permanent cure would have ensued.

There are 5 other cases in our series in which a diagnosis of benign goiter was made and in which operation was advised at the time of the original examination but was deferred. At operation, a malignant tumor was found in each case, and in the majority of these, the tumor was so extensive that complete removal was impossible.

### CARCINOMA OF THE THYROID GLAND

Four per cent of all nodular thyroid glands which are removed surgically are found by the pathologist to contain malignant tumors, and in only 50 per cent of the cases in our series was malignancy suspected at the time of the clinical examination. Therefore, an unsuspected malignant tumor is present in 2 per cent of the cases of nodular goiter that come to operation.

The diagnosis of malignancy of the thyroid is made by observation of the hardness or of the fixation of the gland. The first of these two classical signs is present only when the tumor which originates within the gland has enlarged to such an extent that it begins to involve the palpable surfaces; fixation, moreover, occurs only after the tumor has extended through the capsule. In short, the diagnosis of malignancy of the thyroid gland is usually possible only after the disease has progressed beyond the stage of curability.

In substantiation of this statement, an examination of the case records of 100 malignant tumors of the thyroid gland shows that the permanent cures are more than three times as common in those cases in which the preoperative diagnosis of malignancy was not made as in those in which it was made before operation.<sup>4</sup> Therefore, if we are to cure malignant tumors of the thyroid, we must take advantage of the earliest sign, *i. e.*, enlargement of a discrete adenoma and we must not wait for the classical signs of cancer to develop. An enlarging adenoma should be removed prophylactically just as a breast tumor

should be removed before the clinical signs of malignancy develop.

### HYPERTHYROIDISM

The treatment of hyperthyroidism is subtotal thyroidectomy. Temporization with iodine medication or with  $x$ -ray therapy is particularly undesirable in the presence of a nodular type of goiter. If early operation is performed, the disability is shorter, the cure permanent and the safety is maximum. If operation is delayed, the condition of the patient becomes serious and operation, although affording the only hope of cure, may be rendered dangerous.

### INTRATHORACIC GOITER

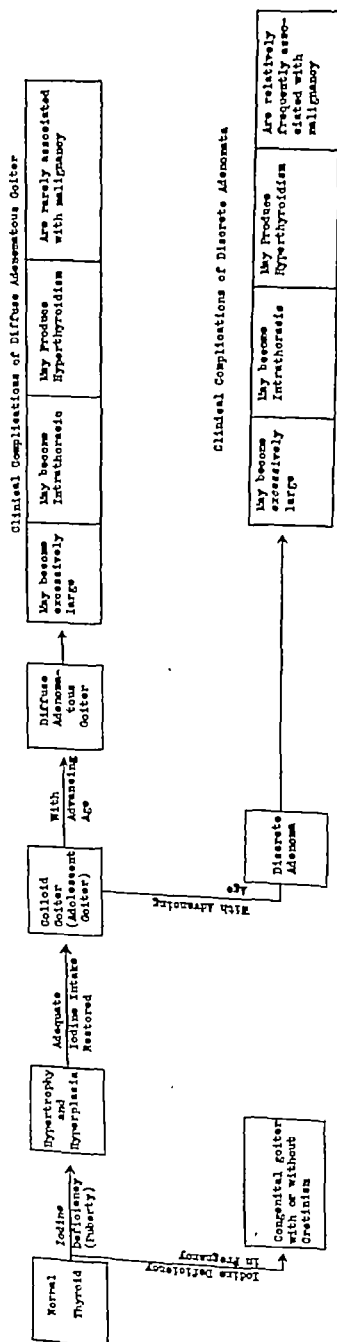
An intrathoracic goiter is rarely an aberrant gland but is almost always an adenoma which has grown downward or has been pushed downward into the thorax. As a rule, such an adenoma continues to grow slowly until finally, symptoms of tracheal or of venous obstruction occur. These symptoms usually become progressively more distressing to the patient until surgical relief finally is sought.

The removal of an intrathoracic goiter is not much more difficult than a simple thyroidectomy when the intrathoracic portion is small enough to be delivered through the outlet of the thoracic cage. The danger associated with this operation is encountered when the gland cannot be delivered except by morcellement. The necessity for such a relatively dangerous procedure could be obviated if the diagnosis were established by  $x$ -ray at the time when the symptoms first appeared, and if the surgical removal of the gland were not delayed.

### CONCLUSIONS

Adenomata of the thyroid are the result of iodine deficiency. All intrathoracic goiters, all large goiters, more than 90 per cent of all malignant epithelial tumors of the thyroid gland, and 50 per cent of all the cases of hyperthyroidism have their origin in adenomata. Since a deficiency in iodine is easily preventable, the responsibility for the prevention of these dis-

THE CLINICAL EVOLUTION OF THYROID DISEASE AS RELATED TO IODINE DEFICIENCY





eases rests with the family physician. If the full cooperation of the patient could be obtained, and if all families were under the care of competent and well-trained physicians, the public could be taught the dangers of iodine deficiency and the incidence of serious thyroid disease could be reduced to at least 40 per cent of its present frequency.

It is important that the physician should know exactly what therapeutic results can be expected from medical treatment of thyroid disease, and that he should realize that in many instances, attempts at medical management result only in delay which jeopardizes the chances of surgical cure.

The diagram on page 1723 will emphasize the rôle of iodine deficiency in the production of diseases of the thyroid gland.

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## THE MANAGEMENT OF COMPLICATING FACTORS IN HYPERTHYROIDISM

A. CARLTON ERNSTENE

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THE most effective treatment of hyperthyroidism consists of subtotal thyroidectomy during an iodine remission. In certain instances, however, the general condition of the patient and the severity of the disease may necessitate preliminary ligation of the superior thyroid arteries or limitation of the operation to the removal of one lobe of the thyroid at a time. Hyperthyroidism is complicated occasionally by the presence of other conditions. These complications do not affect the need for controlling the thyrotoxic state, but frequently they have an important influence upon preoperative and postoperative care and the decision as to the exact manner in which surgical treatment is to be carried out.

### CARDIAC COMPLICATIONS

Dyspnea on exertion, tachycardia and palpitation are present to a certain degree in practically all thyrotoxic patients. In the absence of signs of congestive myocardial failure, however, these symptoms are not to be regarded as evidence of cardiac damage or of myocardial insufficiency, but rather as direct manifestations of the hyperthyroid state. They therefore require no treatment aside from the usual measures employed in preparing the patient for operation.

In certain individuals more important cardiovascular symptoms and signs are observed. Disturbances of heart rhythm occur in 10 or 15 per cent of all patients with hyperthyroidism. The most common abnormal rhythm is auricular fibrillation, although auricular flutter, auricular paroxysmal tachycardia and premature beats are observed at times. Auricular fibril-

lation may be present continually or in paroxysms of long or short duration and may occur in thyrotoxic individuals who have perfectly normal hearts. The arrhythmia is uncommon, however, in patients less than forty years of age, and in the great majority of persons above this age in whom it occurs, hypertension is present or the possibility of changes in the coronary arteries cannot be excluded. If the irregularity is present for a considerable length of time in untreated thyrotoxicosis, the myocardial reserve may be exhausted and signs of heart failure, such as pulmonary congestion, increased venous pressure, engorgement of the liver, dependent edema and orthopnea may develop. Myocardial failure occurs in only a small proportion of patients with hyperthyroidism, but in more than three fourths of the cases in which it does develop, uncontrolled auricular fibrillation has been present for some time. When congestive failure occurs in the presence of normal cardiac rhythm, the patient usually is over forty years of age and some complicating factor such as hypertension, arteriosclerosis or valvular heart disease is present. Myocardial failure with normal cardiac rhythm is extremely rare in young hyperthyroid subjects even though valvular heart disease is present.

An occasional patient with hyperthyroidism experiences attacks of angina pectoris. The first seizure of anginal pain usually occurs after the onset of active hyperthyroidism, although at times a history of earlier attacks is obtained. Hyperthyroidism *per se* probably is not capable of causing angina pectoris, and when patients with thyrotoxicosis experience attacks of anginal pain, the existence of some organic change in the heart, usually sclerosis of the coronary arteries, must be assumed.

The presence of cardiac arrhythmia, congestive myocardial failure or angina pectoris in patients with hyperthyroidism is not to be regarded as a contraindication for surgical treatment. In active thyrotoxicosis unaided medical management of these complications gives unsatisfactory end-results even though a period of temporary improvement may be obtained. Control

of the hyperthyroidism, on the other hand, usually results in complete or practically complete relief from all signs and symptoms referable to the cardiovascular system.

Careful preoperative treatment of the thyrotoxic patient presenting cardiac complications is of course of fundamental importance. As in persons with uncomplicated hyperthyroidism, the treatment consists of absolute rest in bed and the administration of a high calorie diet, Lugol's solution and sedatives. Large amounts of fluids are given except in the presence of myocardial failure. These measures alone frequently result in complete relief from all cardiovascular symptoms and in disappearance of the signs of mild congestive failure. Digitalis is administered only to patients with auricular fibrillation or myocardial failure. Additional therapeutic measures are seldom needed, although occasionally it may be necessary to administer a diuretic drug such as salyrgan. Usually the patient can be prepared for operation in from ten to fourteen days.

In approximately one half of all patients with hyperthyroidism and auricular fibrillation, the heart rhythm spontaneously becomes regular during the early part of convalescence following subtotal thyroidectomy; and in a majority of the remaining patients, normal rhythm can be restored by the oral administration of quinidine sulphate. Spontaneous reversion from auricular fibrillation to normal rhythm usually occurs within the first ten days after operation, and quinidine is employed only when the arrhythmia persists beyond this period. On the first day on which the drug is administered, 2 doses of 3 grains each are given two hours apart in order to determine that the patient is not hypersensitive to it. On the following day, 5 doses of 6 grains each are administered at intervals of two hours. The same amounts are given on subsequent days, but if normal rhythm is not re-established after one week, treatment is discontinued. Usually, however, the arrhythmia is terminated during the first or second day of full dosages. The drug is not administered to individuals known to be hypersensitive to quinine or to patients who have mitral stenosis. In the latter patients,

reversion to normal rhythm is attended by a definite risk of serious accident due to embolism.

The development of auricular fibrillation after operation is generally a complication of but little clinical importance. The irregularity usually lasts for less than forty-eight hours and rarely causes circulatory embarrassment. Normal rhythm almost always is reestablished spontaneously, and in all but a few cases no treatment is necessary. It has been our practice, however, to begin gradual digitalization with the onset of the arrhythmia so that the complete effect of the drug can be obtained more readily in the rare instances in which mild congestive failure does develop. If the arrhythmia should persist for more than ten days, quinidine may be used to restore normal rhythm.

#### DIABETES MELLITUS

Alimentary hyperglycemia and glycosuria occur not infrequently in patients with hyperthyroidism and are of no importance. One should make certain in each instance, however, that diabetes mellitus is not present. The differentiation can be made by measurements of the blood sugar content two hours after a meal or by the glucose tolerance test.

Diabetes mellitus is found to be present in approximately 2 per cent of all patients with hyperthyroidism. Although the presence of this condition frequently is not discovered until *after* the onset of hyperthyroidism, it is generally accepted that hyperthyroidism is not a direct cause of diabetes. Hyperthyroidism, however, causes a decided increase in the severity of preexistent diabetes, and it is probable that the development of frank diabetes *after* the onset of hyperthyroidism is due entirely to accentuation of a latent or previously unrecognized diabetic state.

The preoperative treatment of patients with hyperthyroidism and diabetes differs from the management of uncomplicated thyrotoxicosis only in that the diabetic patient frequently must be given rather large doses of insulin in order to accommodate the customary high calorie diet. Carbohydrates usu-

ally are given in amounts of 150 Gm. or more daily. Measurements of the blood sugar content should be made before each meal. Patients with hyperthyroidism and diabetes are more susceptible to hypoglycemia than are individuals with uncomplicated diabetes, and a close watch therefore must be kept for symptoms of this condition. It is important to bear in mind in this connection that, as an iodine remission is established, carbohydrate tolerance improves, and the dosage of insulin usually must be reduced. During the first few days after operation, it is often necessary to increase the dosage of insulin once more; after this, progressive improvement in the diabetic state generally occurs, and in many patients the use of insulin can be discontinued entirely within a relatively short time.

#### ARTHRITIS

A rather rare complication of hyperthyroidism consists in the development of a condition similar in all respects to idiopathic rheumatoid arthritis. The shoulders and the joints of the fingers are most commonly affected, although at times there may be involvement of practically all joints of the body. Examination reveals thickening of the periarticular tissues with local tenderness and limitation of movement which at times may be extreme. In advanced cases, flexion deformities and varying degrees of muscle atrophy develop. Roentgen examination fails to reveal gross bone or joint changes except for the presence of atrophy.

Physiotherapy and other therapeutic measures commonly employed in rheumatoid arthritis have no appreciable effect upon the arthritis which develops during hyperthyroidism. The induction of a remission in the thyrotoxic state by the administration of iodine also fails to improve the condition of the joints appreciably, and surgical measures such as ligation of the superior thyroid arteries or lobectomy, which only partially control the hyperthyroidism, likewise are of little or no benefit. Subtotal thyroidectomy after the usual preoperative management is followed, however, by prompt improvement. Within forty-eight hours after the operation there is frequently

a decided increase in the range of painless movement in the involved joints, and subsequently a majority of the patients experience gradual but eventually complete or practically complete recovery from the joint manifestations.

In persons in whom rheumatoid arthritis is present prior to the onset of hyperthyroidism, the joint symptoms usually are increased by the development of thyrotoxicosis and are benefited by subtotal thyroidectomy.

### PSYCHOSES AND PSYCHONEUROSES

Hyperthyroidism is complicated at times by the development of definite psychotic states. Usually, in such instances, the thyrotoxicosis is quite severe, although exceptions to this are encountered. The most common psychosis is a toxic delirious mania but occasionally a schizophrenic state occurs. In other patients, severe psychoneuroses without frank psychoses develop during hyperthyroidism. It is probable that the constitution and temperament of the individual are important factors in determining the type of mental disturbance to be precipitated by thyrotoxicosis.

The prognosis in patients who present psychotic or severe psychoneurotic manifestations during hyperthyroidism is always unsatisfactory. Surgery of any kind usually is inadvisable so long as active symptoms are present, because even ligation of one superior thyroid artery may result in a serious increase in the severity of the symptoms and the development of a "hyperthyroid crisis." Roentgen-ray therapy also is contraindicated since it almost invariably increases rather than ameliorates the symptoms. It has been our experience that the most satisfactory course of treatment consists of carrying out the usual preoperative measures, for a period of months if necessary, until the mental symptoms subside. The patient should be kept at absolute rest in bed, sedatives should be employed freely, and large amounts of fluid should be given. Lugol's solution should be given in somewhat smaller amounts than are customary in uncomplicated hyperthyroidism—a daily dose of 5 minims is sufficient. Blood transfusions often are

of help in the severe cases. Even after the mental symptoms have been controlled, operation is attended by a definitely increased risk. Postoperative crises are common and are liable to be attended by a return of the psychotic or psychoneurotic manifestations. It is usually advisable, therefore, to carry out the operative procedures in stages, beginning frequently with preliminary ligation of the superior thyroid arteries. Postoperative management is of even more importance than in patients with uncomplicated hyperthyroidism. The patient should be placed in an oxygen tent immediately, sedatives should be given as necessary, and the intake of fluids should not be less than 3000 cc. per day. Physiologic solution of sodium chloride should be administered by hypodermoclysis in amounts sufficient to keep the total fluid intake at this level. Lugol's solution should be continued for several days. A rise in temperature to above 102° F. is combated by the application of ice bags or ice packs. Transfusion should be performed upon the first appearance of mental symptoms.

#### PULMONARY TUBERCULOSIS

Pulmonary tuberculosis is rarely encountered in patients with hyperthyroidism, and when the two diseases do occur together, the pulmonary condition usually runs a mild course. In these patients, active pulmonary tuberculosis antedates the onset of hyperthyroidism and does not appear to be adversely affected by the development of the thyrotoxic state. The treatment of hyperthyroidism in individuals with tuberculosis is the same as in patients with uncomplicated thyrotoxicosis.

#### PREGNANCY

During the latter part of normal pregnancy, a slight elevation in the basal metabolic rate usually develops, but rarely does this amount to an increase of more than 20 per cent. The rise is not accompanied by symptoms or signs of hyperthyroidism and is of no clinical significance. The rate returns to normal within a few days after delivery.

The development of active hyperthyroidism is an unusual



complication of pregnancy, but the fact that the patient is pregnant does not alter the principles of treatment of the thyrotoxicosis. Ideal treatment consists of subtotal thyroidectomy during an iodine remission. The course of gestation is seldom affected by the operation, and there is no need for terminating pregnancy as a preoperative measure.

#### SUMMARY

With the exception of the psychoses and severe psychoneurotic states, the complications which have been considered seldom affect the prognosis of hyperthyroidism to an important degree. Careful attention to details is necessary during the period of preparation for operation, and in certain instances the period of preoperative treatment must be prolonged beyond the time required in uncomplicated cases. Surgical treatment occasionally must be carried out in stages, and in patients with certain cardiac disturbances, diabetes mellitus or mental symptoms, extra precautions must be taken during the early postoperative period. Careful planning along these lines has resulted in a considerable reduction in the mortality rate of hyperthyroidism and, in this respect, is to be rated second in importance only to the routine preoperative use of iodine.

## ATYPICAL HYPERTHYROIDISM

E. PERRY McCULLAGH

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THE differential diagnosis of hyperthyroidism is usually considered from two widely divergent points of view. On the one hand are cases in which hyperthyroidism does not exist, but the disease is simulated by other conditions such as neuro-circulatory asthenia, the neuroses of the menopause, weight loss of obscure origin or at times by elevated basal metabolic rates of nonthyroid origin.<sup>1</sup> On the other hand are those cases in which hyperthyroidism *does* exist, but for various reasons may simulate other diseases. The first group assumes clinical importance, since the wrong diagnosis may lead to unnecessary thyroid surgery, while the second group is perhaps more important, since a failure to arrive at the correct diagnosis may deprive the patient of the benefits of such surgery as may be necessary to preserve health or life. The second group will be considered here.

One outstanding and simple reason why atypical hyperthyroidism may remain undiagnosed is that the condition is not suspected or not considered seriously enough in the differential diagnosis. The importance of this simple fact is apparent when we consider that the majority of cases of hyperthyroidism of clinical importance are associated with an elevated basal metabolic rate. However, since the basal metabolic rate is not ordinarily determined unless a metabolic or endocrine disorder is suspected, it remains important that we bear in mind the types of cases in which we may be misled. Neither is the basal metabolic rate always elevated, so that in questionable cases we should be prepared to depend entirely upon clinical evidence.

Cases of atypical hyperthyroidism may be considered in three main groups:

I. Hyperthyroidism in which symptoms and signs relating to one system are unusually prominent, thus producing a clinical picture which simulates a disease of a single system.

II. Hyperthyroidism in which one or more of the commonest symptoms or signs are lacking.

III. Hyperthyroidism complicated by another condition which dominates the clinical picture.

#### I. HYPERTHYROIDISM WITH SIGNS RELATED CHIEFLY TO ONE SYSTEM

(A) **Cardiovascular System.**—The most common type of patient with atypical hyperthyroidism in this group is the so-called "thyrocardiac." These patients are usually women over forty years of age who have a visible or palpable nodular goiter, but in a few cases there may be no palpable thyroid enlargement. The history will usually disclose symptoms of mild cardiac decompensation which have been present for a period of months or perhaps years. Repeated attacks of fibrillation may have occurred, a few cases of flutter have been reported,<sup>2</sup> cases are seen which may masquerade for long periods of time as myocardial degeneration or hypertensive heart disease, and a diagnosis of mitral stenosis may have been made. Not infrequently, a middle-aged patient, usually with a goiter, will present herself showing all the evidences of cardiac decompensation which is unassociated with any other signs, and at first, the presence of hyperthyroidism may not be suggested. As in mitral stenosis, the cardiac dulness is increased to the left, the pulse may be somewhat rapid at rest, auricular fibrillation may occur, the sounds usually will be loud and snapping, a thrill or vibration may be felt at the apex, and a systolic murmur often can be heard at the apex, the base, or both; unlike mitral stenosis, however, no diastolic murmur is found.

In some cases, a low serum protein which is apparently closely associated in itself with long-standing hyperthyroidism<sup>3</sup> may aggravate a tendency to edema. In almost all instances

of this sort of hyperthyroidism persistently high basal metabolic rates can be found. The response to iodine medication in such cases is not always convincing. Even when the decompensation is severe enough to necessitate that the thyroidectomy be performed in stages, entirely under local anesthesia and with the patient in the sitting position, the results will often be extremely gratifying. In the light of recent advances in our knowledge regarding the value of complete thyroidectomy in cardiac disorders of nonthyroid origin, one is forced to question whether in all the patients who formerly were improved following thyroidectomy, the cardiac damage was due entirely to thyroid disease. In some of these cases, factors such as arteriosclerosis or other impairment of the myocardial strength may have played a part, although in most instances, as stated above, a basal metabolic rate of plus 30 per cent or above argues strongly in favor of thyroid disease as the chief etiologic agent. Though the clinical conception of the thyrocardiac is undoubtedly useful, it should be remembered that present evidence favors the view that permanent organic damage does not occur to the heart as a result of thyroid disease alone, so that even in the case of severe cardiac failure from thyroid disease, if the heart is relieved of its burden of excessive work it may assume complete normality of function.

Occasionally an individual past forty years of age may be seen who has an adenoma of the thyroid associated with tachycardia. The metabolic rate may be slightly, if at all, elevated, and other evidences of hyperthyroidism may be almost completely absent. When other causes of tachycardia can be excluded, removal of the adenoma may allow the heart rate to return to normal.

(B) **Neuromuscular System.**—The neuromuscular system may produce practically the only signs of hyperthyroidism. A man forty-five years of age has recently come to our attention in whom muscular weakness and severe, coarse, visible tremor of the limbs and entire trunk were the chief symptoms. Because of weight loss of 10 pounds in eleven months associated with a good appetite, hyperthyroidism had been

questioned and the basal metabolic rates were plus 37 per cent, plus 29 per cent and plus 18 per cent. There was, however, only questionable thyroid enlargement and with the exception of six preoperative days in the hospital, the pulse rate had been below 90. Because of the extremely marked tremor, the relatively normal thyroid size and pulse rate, and in spite of the elevated metabolic rate, the surgeons in charge were about to refuse the patient operation. Further observation showed that he was losing weight on a diet of 2500 calories per day while at rest in bed, and it appeared to some of us that the facial expression of the patient, his restlessness and mental irritability, his moist warm skin and loud snapping heart sounds were sufficient to warrant the diagnosis of hyperthyroidism. This opinion was corroborated by prompt recovery following partial thyroidectomy.

Elderly patients with adenomatous goiters or occasionally with little or no thyroid enlargement may be seen at times with a chronic low-grade hyperthyroidism of a type similar to that described above. The facial appearance may be more suggestive of fatigue than of stimulation (the so-called "apathetic hyperthyroidism"<sup>4</sup>) and most of the evidences of hyperthyroidism may be lacking. Muscular weakness and gradual progressive weight loss may be the only symptoms of consequence. Here again, the chief concern is the serious consideration of the possible presence of hyperthyroidism. A careful survey of symptoms, signs, and laboratory data, special tests or trial on iodine will seldom fail to lead to the correct diagnosis. Lahey<sup>5</sup> has warned against the tendency to high postoperative mortality in such cases and suggests the frequent use of the two-stage operation, a single lobectomy being done on each occasion a few weeks apart.

(C) **Disorders of Metabolism.**—Weight loss is seldom if ever the only presenting evidence of hyperthyroidism, but it may be the most evident sign. If there is no obvious cause for weight loss and the diabetes can be excluded, hyperthyroidism deserves careful consideration.

(D) **Ophthalmic Disorders.**—Eye signs may be the only

presenting evidence of hyperthyroidism for some months, but this apparently is a rare occurrence. In one instance, a woman complained only of widening of the left palpebral fissure. No other evidence of hyperthyroidism could be demonstrated during two and a half months of observation, at the end of which time visible and measurable evidences of involvement of the opposite palpebral fissure began to be apparent. The basal metabolic rate at this time was plus 15 per cent. Although there was only questionable enlargement of the thyroid gland, thyroidectomy was advised and performed, following which the eye signs disappeared.

(E) **Gastro-intestinal System.**—Diarrhea occurs in the course of hyperthyroidism in some cases. Shirer<sup>6</sup> demonstrated that hypermotility of the gastro-intestinal tract was present in 92.5 per cent of 42 cases studied by x-ray, the presence of hypermotility being based on the advance of the head of the barium meal to the cecum or beyond in three hours. Diarrhea in the presence of hyperthyroidism has been seen in this clinic less frequently recently than it was previous to six or eight years ago, and my associates cannot recall a single case in which gastro-intestinal symptoms were the only clinical evidence of hyperthyroidism.

## II. HYPERTHYROIDISM IN WHICH ONE OR MORE OF THE COMMONEST SYMPTOMS OR SIGNS ARE LACKING

Some of the most striking features of hyperthyroidism such as tachycardia, goiter, hypermetabolism and weight loss may be absent in some cases.

When tachycardia and elevation of the basal metabolic rate are not found, it may be difficult to know whether their absence is an unusual feature in the particular case in question or whether it is simply an evidence of a natural or induced remission of hyperthyroidism. Continued observation may supply the answer, but such observation is not always feasible.

A normal pulse rate in the presence of active hyperthyroidism is an uncommon finding, and I doubt whether statistics would be of real value. I have not seen it in young people

except in cases of remission and the striking instances which I have observed have been in men past middle age. In some instances, the tachycardia observed while the patient is being examined may disappear after one day in the hospital, so that one does not see the typical pulse curve of hyperthyroidism, which following treatment gradually falls within from one to three weeks. Occasionally, a pulse rate which was about 70 preoperatively, will be reduced to perhaps 50 following the disappearance of hyperthyroidism.

The thyroid gland may not be visibly or palpably enlarged in the presence of hyperthyroidism.<sup>7</sup> If other features of the disease are present, this fact should not deter one from making the diagnosis and applying all the usual methods of therapy.

Most writers agree that hyperthyroidism does exist without an elevated basal metabolic rate even apart from such an occurrence in cases of remission. It occurs most commonly in patients with nodular goiter and therefore in women past middle age. In such instances, it appears that a chronic low-grade hyperthyroidism which has been present for a long time may become burned out so far as a metabolic response is concerned and yet other clinical evidences of the disease may remain. We agree with Morris<sup>8</sup> that the metabolic rate should be *disregarded entirely where there is clinical evidence of thyrotoxicosis and when a goiter is present*. If neither goiter nor elevated metabolic rate are present, extreme caution is necessary in arriving at a diagnosis of thyroid hyperactivity.

It should be borne in mind that symptoms of hyperthyroidism and hypothyroidism may be peculiarly intermingled in some cases; localized myxedema in individuals with hyperthyroidism has never been adequately explained. In one of my cases, remissions in the course of hyperthyroidism were so complete as to be associated with basal metabolic rates of minus 25 per cent and clinical evidence of hypothyroidism requiring the use of desiccated thyroid. This patient later had definitely elevated basal metabolic rates and all the clinical signs of hyperthyroidism again. It is possible that such extreme remissions may explain some of the cases in which the

oral use of thyroid preparations is purported to have caused hyperthyroidism.

In all cases where the basal metabolic rate is normal, the diagnosis of hyperthyroidism must be made with caution. The final results of operation in such instances suggest that diagnostic errors are frequent. Gordon and Graham<sup>9</sup> report 71 cases of hyperthyroidism associated with normal basal metabolic rates, 17 of which were associated with diffuse goiters and 54 with nodular goiters. Operative cures were secured in only 53 per cent of the first group and 66 per cent of the second with improvement in 35 per cent and 18 per cent respectively.

Persistent weight gain in the presence of active hyperthyroidism may occasionally be seen. This occurs at times in young individuals in whom a voracious appetite more than compensates for the tendency to weight loss incurred by elevation of metabolic rates. As a rule, the diagnosis in such instances is clear.

### III. HYPERTHYROIDISM COMPLICATED BY ANOTHER CONDITION WHICH DOMINATES THE CLINICAL PICTURE

Neurocirculatory asthenia is the one condition which perhaps is mistaken most frequently for hyperthyroidism. It occurs in young individuals and is usually marked by the symptoms of nervousness, fatigue and palpitation. Goiter is not an infrequent accompaniment. In neurocirculatory asthenia, the features which ordinarily serve to distinguish the condition from hyperthyroidism are cold, wet, sometimes cyanotic hands and feet, the relatively great variability in the pulse rate, more pronounced signs of sympathetic nervous instability than are usually present in hyperthyroidism, and the general neurotic attitude of the individual. Even the basal metabolic rate may be misleading, at least temporarily, since it tends to vary in the same way as the pulse rate, being perhaps 15 or 18 per cent above normal on one or more occasions. Mild hyperthyroidism supervening in such an individual



may be completely masked and may defy careful scrutiny. A gradual change in facial expression, persistent elevation of the systolic pressure and persistent tachycardia at rest and on repeated observations may serve to put the clinician on his guard. Persistent elevation of the basal metabolic rate above plus 20 per cent or the repeated finding of blood iodine levels of from 15 to 18 micrograms per 100 cc. are useful corroborative evidences. In these cases, operative interference may give only partial symptomatic relief, the hyperthyroidism disappearing, but the neurocirculatory asthenia remaining.

Since arterial hypertension may simulate hyperthyroidism its presence may also "mask" hyperthyroidism. The hypertensive patient may have a flushed face and a mild tachycardia may be highly suggestive of thyroid disease and although an elevated diastolic pressure is not caused by hyperthyroidism neither does its presence exclude the disease. The persistently elevated basal metabolic rate present in some cases of hypertension has not, I think, been adequately explained. If after careful observation and therapeutic trial on iodine there is still real cause for doubt, it may be wisest to err (especially in the presence of goiter) on the side of hyperthyroidism and allow the patient what benefit can be obtained from operation.

Organic heart disease may produce evidence which may direct the clinician's attention away from hyperthyroidism. If a goiter is present and even in the face of decompensation and obvious organic heart disease, hyperthyroidism deserves careful consideration. Here the basal metabolic rate and careful consideration of the possible presence of hyperthyroidism will serve to make the diagnosis clear and elimination of thyroid overactivity will give most gratifying results in most instances.

Menopausal symptoms may overshadow a mild hyperthyroidism such as so often occurs in the case of the middle-aged woman. In all instances where goiter is present this possibility should be seriously considered, and if large doses of estrogenic substances give less relief than is usually seen, or leave a residue of symptoms, possibly of thyroid origin,

even greater suspicion is warranted. If the metabolic rate is persistently high and the blood iodine distinctly elevated, the diagnosis is clear. In case of doubt, it is wiser to advise the removal of an adenoma than to risk the effects of low-grade hyperthyroidism over a long period of time.

Since diabetes and goiter are both common, it is to be expected that their incidence should coincide somewhat. The frequency of association of the two diseases has never been adequately shown to be greater than would be expected on a basis of the rate of occurrence of either alone. When a diabetic presents himself with glycosuria which may appear adequate to explain his weakness, weight loss or even the nervous restlessness or mild tachycardia sometimes seen, it is easy to forget the possibility of hyperthyroidism. Again, especially when thyroid enlargement is present, hyperthyroidism should not be excluded from the diagnosis except after careful consideration. This is especially important since lowering of the metabolic rate may be followed by great improvement in the severity of the diabetes.

Hyperthyroidism commonly occurs in association with pituitary diseases, especially acromegaly and those clinical syndromes simulating the pituitary-adrenal syndrome or pituitary basophilism. When clinical features of such pituitary disease are present, thyroid abnormality should always be excluded.

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## DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM

C. L. HARTSOCK

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IN spite of the fact that it practically always gives clinical clues that should cause its presence to be suspected, in spite of the fact that there is a simple laboratory test which should confirm or disprove this suspicion, and in spite of the fact that a specific therapy is available which will very quickly give undisputed proof of its presence, thyroid insufficiency still remains one of the most frequently overlooked causes of morbidity. There must be some simple reason why this disease, which responds so readily to treatment, should so often go unrecognized. The patient, anxious to be well, tells his history as honestly and completely as he knows how, while we physicians, zealous to cure the patient, make as complete an examination as in any other case. It is in this manner that the true diagnosis of most diseases is discovered; however, if the patient has hypothyroidism, he too frequently goes away from his physician with only a symptomatic diagnosis such as neurasthenia, nervous exhaustion, anemia, low blood pressure, constipation, etc.

I believe that the following factors are responsible for the difficulty which attends recognition of this disease:

1. The disease is much more prevalent than is generally supposed and it is the basic cause of many symptoms that often are attributed to local disturbances in the various systems of the body, rather than to a general cause.
2. The disease characteristically produces negative symptoms and signs rather than positive ones that call our attention to the presence of organic disease.

3. The onset is insidious. Frequently, it is present for years before the patient is even aware that he does not feel as well as he should.

4. The manifestations of the disease at different age periods vary greatly and the presenting symptoms may be referable to any system in the body so that it is difficult to associate them with one common etiological factor.

5. The textbooks have emphasized the advanced types of hypothyroidism and described some of the cardinal symptoms, but have neglected to mention many of the prodromal symptoms and signs which have been present for years before the characteristic picture develops. Oftentimes, a sufficient degree of thyroid insufficiency to bring out the characteristic picture is never developed, and it is these cases that are most frequently overlooked.

When I realized that I was overlooking this disease entirely too frequently, I quickly discovered that there was only one way to make certain that these cases would not escape recognition, and that was to exclude thyroid insufficiency as a factor in every case rather than to include it as a possibility only if some positive clue suggested its presence. As a result of this decision, exclusion has been carried to such an extent that a normal basal metabolic reading has been disregarded in many cases and the more accurate therapeutic test has been tried. This statement will immediately excite the usual criticism which is made when a person is particularly interested in any specific condition; namely, that he makes a diagnosis of the disease in which he is interested entirely too frequently and thereby overlooks other causes of the patient's disability. In my own case, it was not so much an interest in the disease that led me to adopt this method, but these measures were carried out purely as a means of better recognition of cases of hypothyroidism.

When thyroid insufficiency is present, it causes an incomplete oxidation in the metabolic processes of almost all, if not all, the cells of the body. Depending upon the use of the organs of which these cells are an integral part and upon the

amount of damage to the organ by previous stress, strain and disease, the first effects of the disturbed metabolism usually will be to manifest itself by symptoms referable to some particular system rather than to symptoms referable to the entire body, such as is seen in the more advanced cases. Many vague and puzzling symptoms which otherwise receive purely symptomatic treatment without much result, can be explained and cleared up on this basis.

The different systems of the body will be considered and some of the more pronounced disturbances that can be caused by thyroid insufficiency will be cited. It must be kept in mind that these symptoms and signs are the result of a purely metabolic disturbance and can of course be produced by conditions other than hypothyroidism.

**Central Nervous System.**—Somnolence is a symptom of severe thyroid insufficiency and when it is present the patient is usually in a myxedematous condition. Forgetfulness, lack of concentration and a tendency to procrastinate are also symptoms which appear in a late stage of the disease. Restlessness, nervousness and insomnia are more common in the mild cases. Chronic headache which recurs frequently is also a common symptom. These early symptoms are more the result of the general fatigue and hypotension than the direct results of the metabolic disturbance.

**Ocular System.**—Muscle errors which are due to fatigue of the ocular muscle are very common and these in turn may cause a host of vague secondary symptoms such as dizziness, headache, neuralgia, and many others that we frequently ascribe to neurasthenia. Exophoria which occurs toward the end of the day is the most frequent type of muscle imbalance.

**Ear, Nose and Throat.**—A slight edema of the membranes of the nose and throat may be secondary to hypothyroidism. Allergy, another cause for boggy membranes, usually is more pronounced when it is associated with hypothyroidism. We have observed a very interesting symptom complex which is a result of this edematous condition of the membranes. When the membranes near the orifice of the eustachian tube are

swollen, there is a tendency for the tube to close and the patient complains of the very annoying sensation in the ear which results from this closure. Rather typical of this type of closure of the tube is its tendency to occur and disappear, sometimes several times in the same day. The use of ephedrine and air inflation of the tube give only temporary relief, but adequate treatment with thyroid gives quick and permanent relief. Tinnitus is sometimes due to the same cause. Degeneration of the eighth nerve should be suspected of being due to a thyroid disorder. Swelling of the tongue and chronic hoarseness are late symptoms of myxedema.

**Cardiovascular System.**—Bradycardia should always suggest the presence of hypothyroidism but the pulse rate is an unreliable guide because in many cases it is normal or increased. Thyroid insufficiency is occasionally the sole explanation for myocardial weakness. A clue to this etiological factor is found in the low amplitude of the electrocardiographic tracing. Due to the increased cholesterol content of the blood in the presence of hypothyroidism, it may also be a factor in the production of arteriosclerosis, but no improvement is noted following treatment with thyroid, although in early cases it is possible that the progress might be arrested.

Dyspnea is entirely a secondary symptom, but that very peculiar type of dyspnea which is best described as sighing respiration is occasionally due to hypothyroidism; more frequently, however, it is due to an anxiety state.

**Gastro-intestinal System.**—Obstinate constipation as a result of an atonic colon is a characteristic symptom, but all types of indigestion due to fatigue of the gastro-intestinal tract may be caused or aggravated by hypothyroidism. I observed one very interesting case of sudden periodic vomiting in a young woman. No other explanation for her symptoms was ever found and because of other distinct signs of hypothyroidism and a very low basal metabolic rate, she was treated solely from this angle with complete relief from the vomiting. The explanation for this is not clear.

Achlorhydria seems to occur somewhat more frequently

in hypothyroidism but this is such a common finding in patients past middle age that coincidence would lessen the value of such statistics. Adequate therapy certainly does not cause a return of the hydrochloric acid.

**Genito-urinary System.**—One of the classical mistakes in diagnosis is mistaking a case of myxedema for nephritis because of large amounts of albumin in the urine. I observed such a case recently. The patient's symptoms were of twelve years' duration, and she had been consulting doctors almost continuously up until five years before our examination, when her physicians made a diagnosis of nephritis, gave up all hope for her cure and sent her home from the hospital to die. The patient ceased all medical aid or advice and peculiarly enough, her condition improved, but it was still the most advanced case of myxedema I ever saw. The basal metabolic rate was minus 41 per cent. Improvement on thyroid medication was, of course, startling.

Impotence and sterility both in the male and female should cause one to suspect hypothyroidism. In one case, a woman was unable to carry pregnancies to full term, but after the institution of thyroid therapy, she had two full-term, normal pregnancies.

**Glandular System.**—Polyglandular disturbances associated with hypothyroidism as a minor or secondary feature are very commonly found, but in many cases the entire glandular syndrome is improved by the use of thyroid therapy alone, and this is especially true in ovarian types of menstrual disorders. Great advances have been made in specific glandular substitution therapy but thyroid therapy still remains the most potent and specific. It still is of great value in the treatment of pituitary, thyroid, and ovarian types of polyglandular disorders in conjunction with other indicated hormonal therapy.

**Skeletal and Muscular System.**—Vague muscular aches and pains frequently have their origin in thyroid deficiency. Any tendency toward degenerative arthritis is hastened by a low metabolic state. The disturbance of skeletal growth is well exemplified in the cretin.



**Hematopoietic System.**—A mild hypochromic anemia without any other satisfactory explanation should excite a suspicion of thyroid insufficiency. The marked anemias which were thought to be due to myxedema and which simulate pernicious anemia probably also have some deficiency of the extrinsic or intrinsic factor of pernicious anemia.

**Hair, Nails and Skin.**—Dryness of the hair and skin, brittle and thick, coarse nails, falling hair and premature greying of the hair are very suggestive symptoms of this disease and sometimes give the earliest clues.

**General Symptoms.**—Obesity, both generalized and that localized around the pelvic and shoulder regions is the classical sign which usually directs attention to hypothyroidism; however, a fact which is not so generally known is that many thin individuals who never could gain weight begin to do so immediately when they follow well-regulated and observed treatment for mild thyroid insufficiency.

Localized and circumscribed swellings are frequently of myxedematous origin. Swelling of the extremities with changes of temperature or prolonged dependency suggest an early myxedematous state.

Intolerance of cold and a subnormal temperature is usually found, but several cases of chronic pyrexia have been reported that responded to no therapy other than thyroid. Lack of thirst and hypohidrosis are further suggestive general symptoms.

Many other vague symptoms could be cited that are secondary to the chronic fatigue, decreased cellular function and inadequate oxidation of thyroid insufficiency, but this would only serve to make the picture confusing. If the more important symptoms mentioned above are kept in mind, one or more will stand out prominently enough to cause the condition to be suspected and recognized.

**The variation in the picture of hypothyroidism in the different age groups**—children, young adults, and mature adults, is also confusing. Severe hypothyroidism in the child causes the typical picture of cretinism which presents such a

classical picture and has been so adequately described in every textbook that no further discussion is necessary here. Very little is known, however, about mild degrees of hypothyroidism in children. The difficulty of obtaining satisfactory metabolic studies, the normal variability of children's weight, growth, development and intelligence, and the fear of using thyroid preparations in the growing child has presented many obstacles to the investigation of this problem. Undoubtedly, many of the subnormal childhood conditions about which the mother is much more concerned than the physician eventually will be shown to be due to thyroid insufficiency. Diagnostic criteria are still so limited in this group at the present time that we must wait for further studies before we can attempt to recognize and treat the incipient states of hypothyroidism in children.

Severe hypothyroidism can be present in middle-aged patients with surprisingly few of the classical symptoms. It is in this group that the more bizarre symptoms of thyroid insufficiency which were mentioned above are seen. Patients in the older group usually present at least a few of the symptoms suggestive of the clinical picture of myxedema. Rarely do they show them all.

**Differential Diagnosis.**—Many conditions must be taken into consideration in the differential diagnosis of hypothyroidism but two are especially confusing. The symptomatology of the recently described clinical syndrome, achlorhydric anemia or idiopathic hypochromic anemia, frequently suggests hypothyroidism and unless laboratory studies clearly differentiate the two, it is sometimes necessary to determine whether iron or thyroid replacement therapy is the more specific before the true diagnosis can be determined. Some cases are apparently a combination of both conditions and these do better when both medications are used.

Depressed and exhausted states are especially confusing because the basal metabolic rate is also very low in these conditions and it is difficult to tell whether the exhaustion is the result of the low metabolism or vice versa. It is in this type

of case that the therapeutic trial is of great value in the differential diagnosis. Blood cholesterol studies should be made routinely as a differential diagnostic measure because an increase in this substance in the blood is highly suggestive of the presence of hypothyroidism. Whether the clinical picture, the basal metabolic rate and blood cholesterol definitely point to, or only suggest the presence of thyroid insufficiency, the final answer depends upon the ability of the patient to tolerate the specific substance of the thyroid gland.

**Treatment.**—If the patient has hypothyroidism, he should tolerate the replacement of an amount of thyroid equal to that which is deficient, and there should be a concurrent improvement of the condition, especially in the subjective symptoms. Unless objective signs are outstanding, they respond slower than the subjective symptoms. Similarly, if the diagnosis is erroneous and the patient's symptoms are not the result of hypothyroidism, unpleasant subjective symptoms will soon result from overstimulation of the thyroid, and the treatment should be discontinued or tried again with very small dosage.

Many patients and also many physicians are very reluctant to use thyroid substance because of their fear of inducing hyperthyroidism. While it is true that practically all the toxic symptoms of hyperthyroidism can be reproduced by administering the active principle of the thyroid gland, these symptoms promptly subside when the medication is withdrawn, and I have never seen permanent hyperthyroidism induced by the use of the active hormone. A word of caution to the patient and frequent observation offset all dangers attached to the use of thyroid substance.

In a given case where it is decided to use thyroid treatment, the evidence for the disease may either be conclusive or only suspicious. In the former, any other treatment that the patient may need can be prescribed at the time the original prescription for thyroid is given, but in the suspicious cases, it is advisable to have several weeks' observation when thyroid therapy alone is used. This serves to offset the faulty

observation that improvement was due to the thyroid medication when it may have been due to the other treatment. Psychic improvement which comes so frequently for a few weeks after a visit to a confidence-inspiring physician must also be discounted in judging the effects of a trial thyroid therapeutic test.

Once it has been determined that a deficiency in thyroid exists, the rules of treatment are very simple. It is advisable for the physician to experiment with various brands of thyroid products, finally choosing one that he finds potent and then becoming familiar with what results can be expected with various dosages. The potency of the various brands varies so much that it is difficult to stabilize the patient if the same brand is not used continuously throughout the treatment.

The physician should try to bring the patient's metabolism to normal and maintain it at that level. To accomplish this, the beginning dose should be estimated below the amount that will be thought necessary to bring the metabolic rate up to normal. If this dosage is tolerated satisfactorily, it can gradually be increased at intervals of several weeks until a normal metabolic rate is reached. This can be determined partly by clinical observation supplemented by an occasional test of the basal metabolic rate. When a normal level is reached, it is usually necessary to reduce the dosage slightly for a maintenance dose. Frequently at this point the physician does not impress upon the patient the fact that thyroid therapy is only replacement therapy and not curative therapy. This results in the patient believing he is now normal and discontinuing treatment, so that the former condition of hypothyroidism occurs again. Once a diabetic, always a diabetic, and that is also true of hypothyroidism. Changes in environmental circumstances and geographical locations may affect this statement somewhat but in general it is true. The hypothyroidism that so frequently follows subtotal thyroidectomy for hyperthyroidism differs in this regard from nonsurgical hypothyroidism. In these cases the hypothyroidism may last only a short time, but if it persists for as long as two years after the

thyroidectomy, it is usually permanent and demands constant treatment.

After the maintenance dose has been established, periodic checkings every three to six months are advisable. The thyroid insufficiency may be progressive and it may be necessary to increase the dosage from time to time. The insufficiency may remain stationary but other influences may necessitate a change in the dosage. This is particularly true during pregnancy, following illness and with changes of emotional states and geographical location.

In my experience, the basal metabolic rate does not give a very good indication of the amount of thyroid substance that will be necessary to bring the rate up to normal; therefore, the dosages should be worked out in each individual case by the trial and error method. Some patients who have severe myxedema and a very low reading will respond to moderate doses of thyroid substance, while others whose symptoms are rather vague and whose rates are not much below normal will require very large doses before any benefit is derived. This appears illogical, and it may be possible that in some cases there is some difficulty with absorption from the gastrointestinal tract.

Owing to the great variation in the potency of thyroid preparations, it is difficult to discuss exact dosages unless one speaks in terms of thyroxin, which is rarely used on account of the expense. I rarely start treatment on less than a grain of thyroid extract (American standard) believing that if the patient does not tolerate this dosage, hypothyroidism does not play much part in the production of symptoms. However, in some of the polyglandular syndromes where other glandular preparations are being used also, smaller doses of thyroid may be combined with these to give the best results.

It is better to advise that thyroid medication should not be taken after midafternoon. If the medication is given after the evening meal, it frequently causes difficulty in getting to sleep and some palpitation of the heart when the patient first lies down. This rule does not apply if the patient's occupa-

tion or social life is such that his activities are greatest in the evening.

A slight overstimulation is likely to occur for an hour or so after thyroid medication is taken, especially following exercise, emotional excitement or lying down. This temporary excitement should not be enough indication to decrease or discontinue the dosage, but it is an indication that the patient is approaching a normal metabolism. Mild symptoms of excitement are sometimes annoying to patients however, and owing to the fact that the thyroid hormone cannot be supplied artificially with the regularity of the normal thyroid, it is sometimes necessary to maintain a patient at a metabolic level slightly below normal. As the metabolism approaches normal, the patient's subjective sense of well-being will furnish a better guide to his true condition than trying to maintain an absolutely normal metabolic rate. The test, as it usually is done, is not accurate enough to be an index of absolute normality, and furthermore, it must be remembered that the normal rate for each individual is not the same, some being higher and some lower than the standard normal.

In conclusion, I would like to emphasize the high incidence of hypothyroidism, especially in the so-called "goiter section" of the Great Lakes Region. Hyperthyroidism has long been known to be very prevalent in this location, but the number of patients who suffer with hypothyroidism far exceeds those with hyperthyroidism. If the attention of physicians were attracted as easily to the negative character of the symptoms of hypothyroidism as it is to the positive symptoms of hyperthyroidism, there would be a remarkable decrease in the low-grade morbidity of the health of the community.



## CLINICAL PROBLEMS ASSOCIATED WITH MALIGNANCY OF THE THYROID GLAND

ROBERT S. DINSMORE AND JAMES H. YANT

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MALIGNANCY of the thyroid gland is a clinical diagnosis which is hard to make in the early stages of the disease at a time when surgery plus irradiation may offer a cure. Allen Graham<sup>1</sup> pointed out several years ago and as Robertson Ward<sup>2</sup> emphasized more recently, the incidence of malignancy of the thyroid is greater in those regions where goiter is endemic. Therefore, it is of the utmost importance for practitioners in these regions in which thyroid disease is endemic to make a very careful examination of patients with goiters with a view to ruling out the presence of malignancy.

A very satisfactory classification of malignancy of the thyroid both clinically and pathologically is that given by Graham, and the one upon which we shall base our discussion.

Two types of sarcoma are found: lymphosarcoma and spindle cell sarcoma. Some authorities question whether or not sarcoma ever arises in the thyroid gland, but Graham,<sup>1</sup> Pemberton<sup>3</sup> and Shallow, Lemmon and Saleeby<sup>4</sup> definitely recognize that such does occur, although comparatively rarely. This diagnosis has been made only four times in the course of pathological examinations of 40,000 thyroid glands at the Mayo Clinic, and it has been made in 25 of 20,000 microscopic examinations at the Cleveland Clinic. It is felt that lymphosarcoma probably arises in the lymphoid tissue present in the thyroid, and that spindle cell sarcoma apparently has its origin in the stroma of the thyroid, in the capsule, or in the cicatricial tissue present in adenoma. Sarcoma of the thyroid



usually involves both lobes. These patients give a history of short duration of the tumor and very rapid growth, and they may complain bitterly of choking. The entire organ is firm and fixed, the fixation being due to extension to the adjacent tissues and the mediastinum. Distant metastases are uncommon because the local growth is usually so rapid that there is a fatal termination before metastases are recognizable. However, occasionally there is an exception to this general rule such as in the case reported by Schreiner and Murphy,<sup>5</sup> in which the patient is alive and well fifteen years after x-ray treatment, a palliative operation for relief of pressure having been done previously by Crile.

The malignant adenoma arises in a preexisting adenoma. Unfortunately, only about one half of these cases are diagnosed clinically. In a series of 84 cases of malignant adenoma reported by Dinsmore and Crile, Jr.,<sup>6</sup> the diagnosis was made in one third of the cases and was considered as a possibility in 58 per cent. Only 6 of the patients in this latter group are now alive and without recurrence.

Therefore, the importance of the early recognition of this change cannot be stressed too much. This transformation should be suspected in a middle-aged patient complaining that a nodular goiter which has been present for years has recently commenced to enlarge. It is usually stated that change in size has taken place quite suddenly, although the growth may be relatively slow. Unfortunately, this may be the only sign which is suggestive of the carcinomatous change, and even then it may be too late for effective treatment, because the tumor may have metastasized to distant parts by way of the blood stream, even though the capsule of the adenoma has not been broken nor have the lymphatics been invaded. When this type of neoplasm is in its early stage, the patients usually have no symptoms. The carcinomatous change is usually limited to one lobe or even one adenomatous nodule, although other adenomata may be present. The malignant adenoma will have an increase in its consistency which may be detected by the palpating fingers. As the tumor increases in size, certain

she had always had a full neck, but was quite insistent that this tumor had appeared within the preceding three months.

Physical examination revealed a movable tumor which felt cystic, and gave the impression that there had been a hemorrhage into an adenomatous cyst.

At the time of operation, however, the tumor was found to be completely filled with neoplastic tissue and the pathological diagnosis was malignant adenoma.

A course of x-ray therapy was given, but the patient returned in three months with a recurrence in the incision line. This was removed and was found to have cells of the same type as those noted in the tumor previously removed. Another course of x-ray therapy was given.

The patient returned from time to time and was found to be rapidly losing weight. Roentgenograms of the chest, pelvis, spine and long bones were made, but with the exception of a suspicious lesion in the left humerus, no metastases were found. The patient became very much emaciated and it was felt that she must have generalized metastases which could not be located, and death occurred about eighteen months after the primary operation. Before death, a large hard tumor appeared on the side of the face. This apparently was in the parotid gland.

Scirrhus carcinoma is also very slow growing, but its occurrence is so infrequent and it is so inevitably fatal, that it does not merit a great deal of consideration in this discussion. The papillary carcinoma gradually increases in size, and as stated before, metastasis does not take place until the lesion has broken through its capsule, and then usually only the adjacent lymphatics and lymph nodes are involved. The other two malignant tumors which were discussed, sarcoma and carcinoma-sarcoma, are very rapidly growing lesions of the thyroid, and may cause a fatal outcome within a few months or even weeks.

More than 80 per cent of the carcinomata of the thyroid have their origin in adenoma. About 65 per cent of the epithelial malignancies of the thyroid are malignant adenomata. Papillary carcinoma composes about 13 per cent of the total number of malignancies in the series of cases at the Cleveland Clinic. There were 6 cases of scirrhus carcinoma and 5 of carcinoma-sarcoma.

Hyperthyroidism associated with exophthalmos is a rare occurrence in the presence of malignancy. At the Cleveland

comes more pronounced. The patient will then complain of hoarseness, stridor, dysphagia, and choking. These latter symptoms appear when compression and invasion involve the sheath of the laryngeal nerves, the esophagus, larynx and trachea. With progression of the disease there will be marked fixation of the gland and it will be very firm.

The time when these symptoms appear, of course, depends upon the rate of growth, which in turn is dependent to a great



Fig. 181.—Photograph showing size of tumor which had appeared within the preceding three months.

degree upon the type of malignancy present. The growth of the malignant adenoma is comparatively slow, but unfortunately this tumor may metastasize to distant parts relatively early. Occasionally its growth is surprisingly rapid, as is illustrated by the following case.

**Case I.**—The patient was a woman forty-four years of age who came to the clinic in January, 1927 complaining of "goiter" (Fig. 181). She stated that

Struma lymphomatosa, as described by Hashimoto, is a diffuse lymphoid infiltration of the thyroid resulting in a symmetrically enlarged, firm, hard thyroid. Here, too, the normal contour of the thyroid is not lost, and there is no fixation of the gland to adjacent cervical structures, although there is close attachment to the trachea. The disease usually occurs in women in middle life or later. There are no signs of local inflammation. The correct diagnosis is ordinarily not made clinically, although chronic thyroiditis may be suspected.

When sudden hemorrhage into an adenoma has taken place, the history reveals important points in the differential diagnosis. There may or may not be a history of a previously existing goiter. Usually the patient will relate that after exertion there was a sudden increase in the size of the neck. This may take place over a period of a few hours or a day, and accompanying this there may be symptoms of choking and pressure in the neck. Local tenderness may be marked. The swelling is asymmetrical and confined to one lobe, which frequently is very firm and hard. The tumor, after a few days, begins to subside, and gradually becomes smaller as a result of the partial absorption of the hemorrhagic content of the cyst. The time factor and the decrease in the size of the tumor are most important in the differential diagnosis.

Calcified adenomata may be very confusing from the standpoint of differential diagnosis, because they present the firmness of a malignant adenoma, may have a somewhat irregular contour, and are unilateral. However, there will be no fixation. The differential diagnosis may readily be established with the aid of a roentgenogram, which will show the calcified areas. The radiologic demonstration of calcium in a thyroid tumor is strong evidence against malignancy.

After a diagnosis of malignancy of the thyroid is established, the important question is whether or not the lesion has metastasized. Dinsmore and Hicken<sup>8</sup> have recently reviewed the Cleveland Clinic series of metastatic malignancies of the thyroid. The following chart shows the sites at which metastases occurred:

Clinic only one such case has been found that was associated with suspected malignancy. This patient, in addition to her definite exophthalmos and recurrent hyperthyroidism, presented many of the clinical characteristics of malignant adenoma, but the diagnosis could not be confirmed histologically. Clute and Warren<sup>7</sup> report 4 cases in a series of 226 cases of malignancy of the thyroid.

In our series about 63 per cent of all the malignancies occurred in women. Malignancy usually appears in the fifth and sixth decades of life; however, its occurrence is frequent enough in individuals under thirty-nine years of age that the clinician should keep the possibility of malignancy in mind when examining nodular goiters in young patients. Cases have been reported to occur in the first and second decades of life, and a relatively high percentage in the third and fourth.

It is necessary for the clinician to differentiate thyroid malignancy from acute thyroiditis, chronic thyroiditis as described by Riedel and that described by Hashimoto, from sudden hemorrhage in a benign adenoma, and from calcified adenoma.

A respiratory tract infection usually precedes acute thyroiditis by a few days or weeks. The patient has a symmetrical enlargement of one or both lobes of the thyroid gland and there is no distortion of the contour of the lobe or lobes. Local tenderness is very marked, and there may be a low-grade fever. Not infrequently, symptoms and signs are present which suggest a mild degree of hyperthyroidism.

Riedel's struma usually occurs in patients under 40 years of age who, in many instances, have adenomatous goiters. The outline of the thyroid lobes is destroyed. The disease frequently involves only a localized area or one lobe of the gland. The thyroid becomes adherent to surrounding structures with extensive involvement of adjacent cervical tissues. Local tenderness is frequently noted and pressure symptoms are usually marked. At times it may remain for the pathologist to make the correct diagnosis.

right lower pole of the thyroid about the size of a small hen's egg. This was removed and found to be a tumor of exactly the same type as that removed at the primary operation. The patient was observed from time to time, but returned again three months later (September, 1923) with another recurrence. At this time, a mass occupied a position higher up in the neck adjacent to and including the sternocleidomastoid muscle. This mass was removed, together with a large portion of the muscle. The diagnosis at this time was again malignant adenoma.

In April, 1925 the patient returned with a mass the size of a large marble on the left side which was just posterior to the sternocleidomastoid muscle, extending deeply into the neck and firmly attached to the surrounding tissues. This mass was carefully dissected from the carotid sheath.

In September, 1928 a small nodule was removed from the level of the left sternoclavicular joint. The same type of neoplastic tissue was again found within the capsule.

In October, 1928 two small nodules were removed from the skin above the scar on the left side.

In April, 1930 a small recurrent nodule occurred on the right side of the neck anteriorly, near the midline. This tissue was also removed and the same pathological picture was noted.

The patient returned in September, 1931 with extensive recurrence which involved the clavicle and first rib on the left side and compressed the trachea. No treatment was given at this time.

In May, 1932 there was little change in the mass on the left side of the neck. The general condition seemed excellent and the patient stated that he felt and worked better than he had for years.

In October, 1932 he returned with only a small chink between the vocal cords. The larynx was so twisted that the cords were almost horizontal and breathing was labored.

Examination in August, 1933 showed the trachea and larynx to be smooth, and free of involvement. There was a recurrent mass on the left side of the neck.

In October, 1934 the mass on the clavicle seemed to be no larger; it pulsed, and radiographs showed some osteogenesis and definite limitation of the growth. There was some induration and infiltration of the scar on the left side of the neck. x-Ray therapy was given to the clavicle.

The patient was again seen in April, 1935. He had had several small hemorrhages from the trachea. The growth on the left side seemed to be enlarging to the right and pushing the trachea further to the left. The metastatic tumor in the clavicle was smaller. He was admitted to the hospital in May, 1935 because the bleeding from the trachea had been more profuse. Bronchopneumonia developed and the patient expired about ten days after admission.

Necropsy showed that there had been direct extension of the tumor to the trachea, the left clavicle, sternum, right clavicle, and the first ribs, the left being involved more than the right. There were metastatic lesions in the lungs and liver.

This case illustrates that surgery and irradiation can accomplish a great

## SITUATION OF METASTASES IN THYROID MALIGNANCY

Lungs . . . . .	36
Bones . . . . .	18
Cervical nodes . . . . .	94
Axillary nodes . . . . .	3
Brain . . . . .	5
Liver . . . . .	2
Soft tissues . . . . .	2
Intra-abdominal . . . . .	1

The kidneys, heart and eyes are reported as uncommon sites for metastatic lesions.

Involvement of the cervical nodes can usually be determined clinically. Such involvement, in itself, is not a contraindication to surgical treatment because these lesions can be excised at the same time the primary operation is performed.

Symptoms of cough, dyspnea and hemoptysis in the presence of malignancy of the thyroid should make one suspicious of pulmonary metastasis. There may be no physical findings indicative of such a complication, but roentgen examination of the chest will establish the presence or absence of metastases in the lungs. All degrees of involvement may be present. These may vary from a solitary metastatic nodule to multiple small embolic lesions of the lung which give a roentgenographic impression of an exudative process.

Attention may be called to skeletal metastases by pain or a tumor mass. Here again, roentgen examination establishes the definite diagnosis.

Metastatic or recurrent lesions do not contraindicate x-ray treatment. While a cure may not be effected, the comfort of the patient may be improved considerably and, in some instances, the span of life considerably lengthened, as is illustrated by the following case.

**Case II.**—The patient was a man, forty-six years of age, who had a large tumor on the right side of the neck which had extended to the left of the third rib on the right side. In January, 1916 the tumor was removed, some difficulty being encountered in dissecting it from the thorax. The space left by the tumor became entirely obliterated by the pleura, and the marked engorgement of the veins of the neck disappeared. The pathological report at the time of this operation was malignant adenoma.

Seven years later (June, 1923) the patient returned with a tumor in the

## THE DISEASES OF THE THYROID GLAND AND THEIR RESPONSE TO ROENTGEN AND RADIUM THERAPY

U. V. PORTMANN

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IN order to determine what results may be expected from roentgen and radium therapy for the treatment of different diseases of the thyroid gland, it may be desirable to review briefly some of the effects of radiation upon tissues and apply this information to the pathological conditions in which the thyroid is affected.

### THE EFFECTS OF IRRADIATION UPON TISSUES

The effects of roentgen or radium rays upon tissues is brought about primarily by injury to cells. Normal or pathologic cells, and therefore tissues, vary considerably in their sensitivity or resistance to this damage. One of the oldest basic laws concerning the relative degree to which tissues respond to destruction by radiation states that "immature cells and cells in an active state of division are more sensitive to radiation than are cells which have acquired their adult morphologic and physiologic character." Accordingly, embryonic cells and neoplastic cells which are undergoing cellular division and tissues which are growing may be injured by radiation, while most normal tissues which have attained their physiologic destiny are relatively resistant.

But even neoplastic tissues vary in their radiosensitivity according to their rate of growth and their degree of differentiation or the nearness of their approach to the morphologic and physiologic character of the normal cells from which they originated. Normal tissues may also be radiosensitive or resistant, according to their degree of differentiation from their primordial cells, their reproductive capacity and the specialization of their physiologic function. For example, the leuko-



deal for here was a patient who for nineteen years lived a useful, productive life, even though recurrent and metastatic lesions developed after the original diagnosis was made.

When irradiation is administered it should be given not only at the site of the primary lesion, but also over the areas of the metastases.

Portmann<sup>9</sup> reviewed the results obtained in 222 cases of thyroid malignancy seen at the Cleveland Clinic. In 36 instances where operation was deemed inadvisable, the average length of life of the patients living at the end of the period of observation was forty-one months and of those dead, twenty-seven months. Of 78 cases of proved malignant adenoma, 32 per cent of the patients were alive for an average of six and one quarter years. Papillary carcinoma was present in 15 patients, 9 of whom were alive for an average of six years.

For the most part, the results of treatment in the remaining types of malignant disease of the thyroid gland have not been so favorable. However, these remaining groups compose a very small percentage of the total thyroid malignancies. Therefore, we feel that the outlook for the patient suffering with a thyroid malignancy is better than is generally supposed.

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But even neoplastic tissues vary in their radiosensitivity according to their rate of growth and their degree of differentiation or the nearness of their approach to the morphologic and physiologic character of the normal cells from which they originated. Normal tissues may also be radiosensitive or resistant, according to their degree of differentiation from their primordial cells, their reproductive capacity and the specialization of their physiologic function. For example, the leuko-

cytes which are reproducible and the germinal cells of gonads which are constantly renewed until they are finally exhausted and which are a biologic luxury and not a necessity, are very sensitive to the direct destructive influences of radiation, but brain cells without regenerative power and with highly specialized functions are most resistant.

Important indirect changes are also created in tissues by damage to the radiosensitive endothelial living cells of capillaries and lymphatics. When these cells are affected, they undergo degenerative changes which result in thrombosis of the vessels by cellular débris, exudation occurs and fibrosis eventually causes the tissues nourished by these vessels to become avascular and consequently their activities are curtailed.

In the case of inflammatory tissues, the effect of radiation is also primarily destructive. A good explanation of the *modus operandi* is that the radiosensitive and the phagocytic leukocytes, which mobilize about an inflammatory focus and carry antitoxins, are destroyed, so that an excess of these protective substances is liberated in the tissues and the toxins are neutralized.

As a result of the direct and indirect destructive effect upon cells and the reactions in tissues, radiation may be employed to suppress, modify or abolish physiologic activities of organs, to create reactionary changes which prevent the progressive development of inflammation at certain stages or to inhibit or destroy malignant growth. Therefore, in some constitutional disturbances in which functional derangement of the thyroid seems to play a rôle, or in the presence of inflammation of the gland or neoplastic diseases, the patient may be benefited by roentgen or radium treatment according to the fundamental character of the pathologic process that created the disease condition.

#### THE PATHOLOGY OF NONTOXIC AND TOXIC GOITERS

The thyroid gland undergoes physiologic and pathologic changes which are so closely associated that it may be dif-

difficult to differentiate between the normal and the abnormal on the basis of variations or similarities in the morphologic structure of the gland. The histology which is consistent with some phase of morphologic changes known to be associated with physiological processes may be found under conditions which are distinctly pathological from the standpoint of the clinical manifestations of abnormality. Therefore, much confusion has resulted from attempts to differentiate or classify different types of goiter on the basis of histology alone. The simplest classification takes into consideration aspects of thyroid disease which are evidenced by clinical signs and symptoms of constitutional toxicity or absence of toxicity in which the gland plays some indeterminable rôle. But in the presence of either nontoxic or toxic states, the morphology throughout the glands may be similar.

The morphology consistent with physiologic changes includes hypertrophy, hyperplasia or both, and involution. The pathologic changes are degenerative and include atrophy, fibrosis and inflammation. Varying degrees of any or all of these physiologic and pathologic morphologic changes may be found in a thyroid in association with constitutional manifestations of toxicity or without them, but no single change or combination of these alterations indicate any particular disease.

Those physiologic or pathologic stimuli which cause the thyroid to become enlarged by hypertrophy, hyperplasia or involutional changes produce a "diffuse goiter." The only symptoms from such a goiter may be caused by the gross mass which produces pressure upon neighboring structures or an unsightly deformity of the neck. However, under other indeterminable conditions, the structure consistent with diffuse goiter, with or without much enlargement of the thyroid, may be associated with constitutional disturbances which are recognized as toxic in their effect and which are given many names, such as Graves' disease, Basedow's disease, thyrotoxicosis, hyperthyroidism, dysthyroidism, exophthalmic goiter, or "toxic goiter."

Also in addition to diffuse nontoxic goiters another type of

morphology may be found, and this is manifested by areas which have an adenomatous structure; these areas vary in size from microscopic to clinically palpable nodules. These nodular adenomatous changes may occur without constitutional evidences of toxicity as, for example, in those goiters which have been called simple or endemic or "nontoxic" and also in association with the clinical syndrome of "toxic goiter," which is designated by such names as exophthalmic goiter or toxic adenoma, etc., and which are "nodular goiters." These occur most frequently in adults and may represent an advanced or adult involutional stage following a diffuse type of goiter, and hyperplasia may be present or even predominate in many cases.

Dr. Allen Graham summarizes the matter as follows: "We have found no anatomical, histological, chemical or pathological qualities in adenomata or adenomatous thyroid tissue, such as would furnish a reliable basis for distinction between toxic and nontoxic goiter. We have found colloid adenomata in hyperplastic thyroids, and hyperplastic adenomata in colloid thyroids and this may occur in either toxic or nontoxic goiter."

Since the histology of the thyroid alone cannot be a basis for distinguishing the different types of goiter, the American Society for the Study of Goiter has suggested the division of these functional changes into the nontoxic and toxic goiters and recognizes that either of these two clinical types may be diffuse or nodular goiters from the standpoint of morphology.

#### THE EFFECTS OF IRRADIATION UPON NONTOXIC GOITER

The cells of the thyroid gland are not embryonic, are not in an active state of division, although they may be undergoing involutional changes, and the organ has highly specialized functions. We therefore would not expect normal thyroid cells to be radiosensitive, and this has been proved by clinical and experimental observations. Since either nontoxic or toxic goiters are composed of tissues occurring in normal thyroids and are pathologic because of the influence of extraneous

physiologic processes which create involutional (or degenerative) changes of quantity rather than quality of tissue, or else because the goiter is associated with constitutional disturbances in which the morphology of the gland may be similar to that found under normal conditions, we would not expect therapeutic radiation to change the structure of the organ from one involutional state to another nor to reduce the size of a goiter by direct destruction of thyroid cells. Therefore, irradiation is not indicated for the nontoxic diffuse or nodular goiters because they only represent involutional changes in the gland and except for their bulk, they produce no subjective difficulty. When the size of a nontoxic diffuse or adenomatous goiter is disturbing, it may be treated successfully by medical or surgical measures.

However, we know that irradiation may alter the function of an organ by affecting its vascular supply or by a direct inhibition of cellular physiologic processes and this is especially true of all secretory glands. In the constitutional disturbances associated with either diffuse or nodular toxic goiters, suppression of the activity of the thyroid by irradiation may relieve the symptoms in some cases even though the morphology of the tissue is not materially altered with the possible exception of the production of some degree of fibrosis. The same clinical result is also obtained by removal of a part of the thyroid gland.

#### THE TREATMENT OF TOXIC GOITER

It is not my purpose to discuss the relative merits of surgical operations or irradiation in the treatment of toxic goiter. Usually arguments about the subject are based upon prejudices and simply amount to presentations of the objections to each procedure rather than the benefits. There are numerous reports in the literature which may be reviewed for making comparisons. Radiologists report from 75 to 80 per cent of their patients cured or improved, about 15 per cent have recurrences or are unimproved and a mortality of from 5 to 12 per cent, if all patients are included who died of the disease

after irradiation. It would appear that these results compare quite favorably with the statistics of the surgeons.

**Roentgen Therapy.**—In the treatment of toxic goiter with roentgen rays, the tendency is toward moderate rather than intensive irradiation, the important control factor being the condition of the patient. The indications for the frequency or intensity of individual treatments or series of treatments should depend upon a decrease or increase of symptoms as manifested by changes in the basal metabolic rate, in the pulse rate, loss or gain of weight, and improvement in the subjective symptoms.

The technical and mechanical factors which are employed depend to some degree upon the personal preference or experience of the radiologist. These details are rather unimportant. Moderately penetrating rays are generally preferred, a peak voltage of from 90 to 140 kv. being employed with filtration by from 4 to 8 mm. of aluminum or its equivalent to produce an effective wavelength of from 0.28 to 0.29 angstrom. The milliamperage, time and focal distance from the skin are factors of choice by the individual operator and depend to a great degree upon the intensity of the output by the apparatus employed, of which no two are exactly alike. Most radiologists seem to prefer to administer to each field from 150 to 250 roentgen at each treatment, the dosage being calculated to include back-scattering from the skin.

In order to avoid any great amount of scattered radiation which might damage the larynx and trachea, these organs must be carefully protected. It is customary to irradiate the right and left lobes of the thyroid separately, although this is unnecessary *from the standpoint of actual dose absorbed into the gland.*

Some radiologists also administer the dosage over the mediastinum in order to irradiate the thymic area. The inclusion of this region, although considered important by some radiologists, would seem to be unnecessary in many instances, unless previous radiographs of the chest show the existence of a substernal goiter which might be active or show some evi-

dences of the presence of abnormal lymphatic tissue within the mediastinum. Although thymic tissue may be found in the mediastinum, especially in young individuals, it probably does not contribute to the toxic state, but it is a part of the generalized lymphatic reaction which is always associated with toxic goiter, and therefore the necessity for the routine treatment of the mediastinum is debatable.

The frequency of roentgen treatments depends upon the severity of the symptoms and the reaction in the individual case. In the beginning of a series of treatments, once a week is usually considered to be often enough, or the treatments may be spaced at longer intervals, the average being about two weeks. Usually from 6 to 8 treatments constitute a series. A careful record of the pulse rate, weight and subjective symptoms should be kept, and the basal metabolic rate should be determined before each treatment, the course and dose being governed accordingly. The number of series which may be given will vary with the indications in the individual case, but it would seem advisable to discontinue treatment if decided improvement is not manifested within two or three months.

**Radium Therapy.**—The intensity of radiation with radium, which is administered for toxic goiter, will naturally depend upon the quantity of radium which is available. Usually radium packs are used and about one third of an "erythema dose" is administered to each lobe at each treatment, the trachea being protected. For example, with a  $4 \times 4$  cm. pack at 2 cm. distance and a filter equivalent to 4 mm. of brass, the dose would be 400 mg. hours.

The frequency and intensity of radium treatments should be governed in the same way as in the roentgen-ray treatment.

A few radiologists have employed interstitial radiation by means of radon gold seeds or needles. I believe interstitial radiation is inadvisable because of the necessity for the surgical procedure involved, which is attended by as much hazard as thyroidectomy. Moreover, the radiation effects cannot be controlled accurately because no one can predetermine the exact intensity of radiation which will be necessary to con-



trol the symptoms. If too much thyroid tissue is destroyed, hypothyroidism may result, and if too little is applied, the patient will not be relieved or the treatment must be repeated.

#### THE TREATMENT OF INFLAMMATIONS OF THE THYROID

**Acute Simple Thyroiditis.**—Acute inflammation of the thyroid gland is manifested by the usual symptoms of inflammation, namely, rather rapid swelling, local heat, tenderness, pain and fever. The process may progress to abscess formation. The treatment consists in the local application of cold and of small doses of roentgen rays, which will have an analgesic effect about the inflammation and shorten convalescence. If the inflammatory process has progressed to an abscess stage, the roentgen treatment will hasten the breaking down and drainage incisions may be made very promptly. Therefore, roentgen treatment may be instituted with benefit at any stage of the inflammation, although it is more beneficial when applied early and it is hazardous to administer dosage of great intensity at one treatment.

**Chronic thyroiditis, Riedel's struma or ligneous thyroiditis** is a chronic inflammation of the thyroid gland which is manifested by a quiet painless swelling of fairly rapid growth. The gland is very hard and fixed, and in about one half the cases the condition is bilateral. The obstructive symptoms are prominent very early in the course of the disease. Because of the similarity of the signs and symptoms, it is very difficult and sometimes impossible to differentiate this condition from malignant disease except possibly by the rate of growth. When a clinical diagnosis can be made, roentgen therapy is the preferred treatment. The intensity of radiation which should be applied is somewhat greater than that employed for acute inflammation; however, immediately after the treatment, swelling of the gland may occur which may be relieved by hot applications. When there is marked obstruction a tracheotomy may be necessary.

**Tuberculosis of the Thyroid Gland.**—This produces a more or less chronic inflammation of the thyroid, which is sel-

dom recognized clinically, and is often difficult to diagnose, even by means of microscopic sections. The pathologic process and its manifestations are the usual manifestations of tuberculosis. Tuberculous inflammation of the thyroid may invade adjacent lymphatics and other tissues, and rarely may form a tuberculous abscess. When tuberculosis of the thyroid is recognized, it should be treated by small doses of roentgen rays to relieve lymphocytic infiltrations and create the production of fibrous tissue just as in the case of tuberculous lesions in other localities.

#### STRUMA LYMPHOMATOSA

This is a rare disease of the thyroid which is manifested by the presence of a large amount of lymphatic tissue in the thyroid gland and is associated with some fibrosis and atrophy. Clinically, there is a diffuse, bilateral, quiet and rapid enlargement of the thyroid gland which, in contrast to Riedel's struma or a neoplasm, is not adherent to adjacent structures. There are a few symptoms and no evidence of toxicity but late in the disease some obstructive symptoms may develop because of fibrosis. One patient whom I treated was diagnosed clinically as having an inoperable neoplasm of the thyroid, but one year later, in spite of radiation, the goiter had not decreased in size and the obstructive symptoms were increased. Subsequently an operation was performed and the true condition was recognized. It is probable that radiation treatment of this condition increases the fibrosis and from clinical evidences at least, it is of no benefit.

It is recognized that struma lymphomatosa may develop into lymphosarcoma; when this occurs, intensive radiation is indicated. In such cases radiation may result in relief or cure.

#### MALIGNANT GOITER

Within recent years better understanding of malignant disease has brought the realization that the histologic morphology of tissue is not always a criterion by which neoplasms can be differentiated or classified, and does not always indicate what

trol the symptoms. If too much thyroid tissue is destroyed, hypothyroidism may result, and if too little is applied, the patient will not be relieved or the treatment must be repeated.

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**Tuberculosis of the Thyroid Gland.**—This produces a more or less chronic inflammation of the thyroid, which is sel-

omas of the thyroid which originate in preexisting adenomas, exclusive of the papillary cyst adenomas. He has found that this group constitutes about 90 per cent of all malignant lesions of the gland, and at least 90 per cent of the epithelial thyroid malignancies can be proved to have originated in pre-existing adenomas.

When a preexisting benign adenoma of the thyroid undergoes malignant degenerative changes the growth may present many combinations of morphologic transitions such as fetal, intermediate or mixed colloid adenomas, and any one, two or all of these transitions may be found in a single tumor; in fact, it is seldom that only one type is found. Therefore, adenocarcinoma, medullary carcinoma, scirrhus carcinoma, papillary carcinoma or carcinoma resembling sarcoma or any combination of these forms may develop as a malignant adenoma, or may be found in thrombi within the vessels. Because of this variability of structure, it is difficult to make a diagnosis of the type of growth on the basis of morphology; therefore, before the true character of the neoplasm can be established, it is necessary to study the type of structure of the preexisting adenoma, its duration and rate of growth, the character and reaction of the stroma, and especially the evidence of invasion of the blood vessels.

Malignant adenomas are primarily encapsulated by the connective tissue which surrounds the preexisting adenoma, but since the neoplastic epithelial cells lie in direct contact with numerous blood vessels in and around the tumor, these will be filled with neoplastic cells in almost every instance by the gradual expansion and invasion of the growth. Neoplastic cells may escape into the vessels of the adenoma and metastases may occur by way of the blood stream even though the growth may not have broken through its own capsule. This manifestation in the blood vessels is characteristic and distinguishes malignant adenomas regardless of the histologic structure.

Malignant adenomas are found in patients past middle age in whom goiters, which have been present for a long time, have begun to enlarge rapidly. The progress of the enlarge-

may be their clinical course. This is particularly true of the malignant tumors of the thyroid gland, there being certain points in their origin, development, structure and growth characteristics which are just as important as their microscopic morphology and must be taken into consideration in order to distinguish the different types of growth and to understand the reasons for their peculiar variations. Therapeutic procedures should be planned on the basis of the growth characteristics of each different type of neoplasm.

Certain characteristics of the thyroid gland give indications as to the types of malignant goiter which may occur.

1. Thyroid tissue consists largely of glandular epithelial cells. Hence on the basis of the laws of probability, epithelial neoplasms or carcinomas should occur with proportionately greater frequency than the mesothelial neoplasms or sarcomas.

2. The character of the concentric and hyperplastic development of the thyroid glandular structure predisposes to the production of localized adenomatous tumors which may undergo many kinds of degenerative changes, including malignancy, because of their inherent embryonic stimulus to hyperplastic growth; therefore malignant growths which originate in such adenomatous tumors should occur with relative frequency.

3. The acini of the thyroid have no basement membrane, and because their cells lie in such close proximity to the vessels, they may readily penetrate into the circulating blood and may quickly be distributed to different parts of the body as metastases.

4. The lymphatic distribution and drainage of the thyroid cause the fairly early involvement of the deeper cervical lymph nodes by certain types of malignant processes, and frequently this occurs before the involvement can be determined clinically, and the abundant intracapsular plexus permits direct extension to adjacent structures, particularly to the trachea.

**Malignant Adenomas.**—The term malignant adenoma was suggested by Dr. Allen Graham to designate those carcin-

are sometimes palpably enlarged. They grow very slowly but progressively, and are of low-grade malignancy from the standpoint of rapidity of growth, but they destroy life by local constriction even before metastases develop.

**Papillary Carcinoma.**—Adenomas of the thyroid, like adenomas in other organs, may also undergo cystic degeneration and in turn these cystic adenomas may become malignant. When this occurs, multiple finger-like processes are formed in the walls of the acini in the arrangement which is characteristic of papillary carcinoma. The growth is at first confined within its capsule, but gradually the neoplastic columnar cells of the papillae invade and break through the thin stroma at the base of the acini in which they develop, and thus extend to adjacent acini and the lymphatics. They do not invade blood vessels because the cysts in which they originate are avascular, and because they are primarily encapsulated and confined. As would be expected from the nature of their origin and the character of their growth, these neoplasms are of a comparatively low grade of malignancy. As indicated previously, some malignant adenomas may contain areas with papilliferous formation.

Clinically, the papillary carcinomas are usually unilateral, rather firm, nodular tumors, which grow slowly, but sometimes become very large. As the tumor progresses, the structures about it are infiltrated and compressed, and the skin may become red and edematous with eventual breakdown and ulceration.

**Carcinoma-sarcoma.**—A rare tumor of mixed carcinoma and sarcoma occurs in the thyroid. The epithelial structures show changes characteristic of carcinoma and the abundant stroma presents the appearance of fibrosarcoma. There are numerous mitotic cells arranged atypically in both epithelial and mesothelial elements. Theoretically, this type of tumor may begin as carcinoma which, because of some peculiarity of growth or physiologic reaction, causes neoplastic stimulus to the stroma so that it also becomes malignant. However, there is little proof of the theory. Usually, this

ment may be relatively slow, even with occasional regressions unrelated to any physiologic process. A hard tumor is found in the thyroid, usually unilaterally, but a smooth, firm, general enlargement occasionally occurs, depending somewhat upon the duration and the rate of growth.

A clinical diagnosis can be made in about one half the cases, the others being discovered by the pathologist after removal of thyroid tissue from goiters, supposedly benign.

**Adenocarcinoma Not in Adenoma.**—Occasionally, a peculiar lesion is encountered in the thyroid which may be called "adenocarcinoma not originating in adenoma." This lesion has some characteristics of carcinoma, but is of very low-grade malignancy. It originates in acinar epithelium, remains quite localized, is not encapsulated and no mitotic figures are demonstrable. It might be called "carcinomatoid," and is only of interest to pathologists, because it gives no clinical signs or symptoms, is not fatal and is of no importance to the radiologist.

**Scirrhou carcinoma.**—The kind of stimulus to neoplastic growth which causes a scirrhou carcinoma to develop in the thyroid gland produces the same histologic changes in this organ as are found in scirrhou carcinomas in other structures. Fibrous tissue predominates and the neoplastic epithelial cells occur in masses of strands as though the malignant reaction were held in restraint so that glandular arrangement cannot take place. The growths are not encapsulated and, therefore, progressively invade the surrounding tissues which they destroy by infiltration through the lymphatics and compress the blood vessels in fibrous tissue. It cannot be determined that scirrhou carcinomas of the thyroid begin in adenomas, although there is no reason why they should not do so. As previously mentioned, a malignant adenoma may present localized areas of scirrhou formation along with other types of malignant changes.

These neoplasms seldom are discovered early by clinical examination but in the late stages and after recurrence, they are extremely hard and fixed, and the invaded lymph nodes

particularly in the bases and they gradually enlarge and coalesce as the disease progresses or large solitary tumors may be seen.

Metastases may also occur in bones, especially in the long bones, but also to some extent throughout the rest of the skeletal system. When roentgen examination reveals an otherwise unexplainable, but obviously malignant lesion in a bone, the thyroid should be suspected as the primary source of a neoplasm, even though there may be no other evidence of disease of this organ.

Occasionally, metastases occur in soft tissues as slowly growing tumors without any definite clinical characteristics, and only microscopic examination will disclose their thyroid origin.

Distant metastases are almost always from malignant adenomas. They develop from neoplastic cells which have invaded blood vessels, become detached and are distributed through the circulation and form neoplastic emboli in various locations. Because these metastases have the histologic morphology and probable function of the parent neoplasm which may closely resemble normal thyroid tissues, they have been mistaken for aberrant thyroid rests.

When metastases are present, operations upon the thyroid usually are not indicated. However, even when metastases are present or when the growth has invaded the structure contiguous to the thyroid, it may be necessary to perform a decompression operation to remove some of the growth, or to perform a tracheotomy in order to relieve respiratory difficulty. Roentgen irradiation should be administered following such palliative operations to inoperable neoplasms and to metastases, some of which may thus be held in check for some time.

#### TREATMENT OF MALIGNANT GOITER AND ITS RESULTS

The procedure for the treatment of a malignant tumor of the thyroid should be based upon its known growth characteristics. In only about 50 per cent of cases can a clinical di-



tumor is erroneously considered to be carcinoma, or is occasionally classified as fibrosarcoma, depending upon the type of cells which are found. There is no possibility of differentiating this growth clinically; it must be distinguished by microscopic examination. It appears as a hard, rapidly extending mass in a lobe of the thyroid.

**Sarcoma.**—True sarcomas of the thyroid are rare in spite of the fact that the literature contains many reports of such cases. If the relative proportion of mesothelial elements to the epithelial structures is taken into consideration, it must be realized that sarcomas should be comparatively uncommon. The usual mistake is to call a very cellular, malignant adenoma a sarcoma. However, sarcomas originate in the mesoblastic elements of the stroma, and a study of different regions will usually distinguish them from malignant adenomas by the absence of epithelial cells in the tumor.

The most common type of sarcoma of the thyroid is lymphosarcoma and it has the same characteristics as similar neoplasms in any other organ. The growth is highly malignant and quickly infiltrates the thyroid and adjacent structures. Clinically, patients with lymphosarcoma give a short history of very rapid growth, and usually the entire organ is firm and fixed and the patient complains bitterly of choking. The rapid infiltration of the gland and adjacent structures, particularly extension into the upper mediastinum, usually destroys the host before distant metastases become evident.

Fibrosarcomas, or spindle cell sarcomas, originating in the stroma also are seen occasionally, but they are very rare. They grow more slowly than lymphosarcomas, and clinically are indistinguishable from other tumors.

**Metastases.**—Every patient for whom an operation on the thyroid is contemplated should first have a roentgenographic examination of the chest. Such an examination may reveal unsuspected, benign, intrathoracic or substernal thyroids or metastases from a malignant goiter that may or may not be discovered by clinical examination. Pulmonary metastases usually are seen as a shower of small nodules of various sizes,

very hard growth. It is almost a certainty that such a growth has invaded the lymphatics and other structures contiguous to the thyroid and has extended widely through the lymphatics, and for this reason cannot be entirely excised. Scirrhus carcinomas are highly resistant to irradiation, and since they destroy life before distant metastases develop, interstitial irradiation followed by roentgen irradiation should be administered, although even with this procedure, the prognosis is very bad.

Occasionally, a papillary carcinoma may be so localized and encapsulated that it may be excised completely, but when there is clinical, gross or microscopic evidence or a suspicion that the growth has extended through the lymphatics into the surrounding thyroid gland structure or adjacent tissues outside the field of operation, irradiation should be administered. These growths do not invade blood vessels early as do malignant adenomas, and therefore the application of interstitial irradiation is not so hazardous. If and when this type of growth is recognized at operation, interstitial irradiation may be applied at once, to be followed later by roentgen treatment. If the neoplasm is discovered subsequent to operation, it is advisable to depend upon roentgen irradiation unless the growth continues, and then a second more extensive operation and implantation of radium in one form or another may be necessary. Some of these growths yield to irradiation.

#### TECHNIC OF IRRADIATION

The technic of applying radium to malignant goiters should be planned according to the type and size of growth. The more resistant neoplasms should be given as great an intensity as is possible. Gold radon seeds may be employed but the trachea and large vessels should be avoided in making the implantations. As has been pointed out, it is better not to thrust needles into malignant adenomatous tissue, and so roentgen irradiation should be employed primarily, and this should be followed by interstitial irradiation if necessary.

In administering roentgen irradiation we have been using

agnosis be made before operation; therefore, half of these patients have had some sort of operation and the true nature of the tumor is only discovered by the pathologist.

When a definite diagnosis of malignant goiter can be made by clinical examination, the condition usually is inoperable from the standpoint of curability because of the probability of invasion of the vessels in the tissues which cannot be removed. Sometimes, however, palliative operations are advisable and at least a biopsy should be done to determine the type of neoplasm in order that a logical therapeutic régime may be instituted. In any case, in operating upon a patient with malignancy of the thyroid, the surgeon should always have in mind the possibility of causing embolic metastases by harsh manipulation.

When a malignant adenoma is discovered, treatment is begun with roentgen irradiation regardless of whether or not the surgeon believes he has removed all the growth, because there is always the possibility of invasion of the blood vessels outside the field of operation. Since about 90 per cent of the malignant neoplasms of the thyroid are malignant adenomas, the blood vessels are probably invaded and so interstitial irradiation is seldom employed at the time of operation. This treatment may be used with less hazard after the neoplasm has been rendered dormant by roentgen irradiation, or later, if it is obvious that the roentgen treatment has not been entirely efficacious. Most of the malignant adenomas are quite sensitive to irradiation, not only because the neoplastic cells in the tumor and those in the vessels are radio-sensitive, but also no doubt, because of the secondary fibrosing and obliterating effect upon the capillaries, which prohibits further extension. Roentgen irradiation alone, especially for inoperable tumors, has been quite efficacious in our experience.

The adenocarcinomas not originating in adenomas are so localized and of such low-grade malignancy that none of them require irradiation. Of 17 patients with this carcinomatoid growth, 16 of whom have been traced, all are well.

Scirrhus carcinoma may be recognized at operation as a

## PREOPERATIVE AND POSTOPERATIVE TREATMENT OF THE PATIENT WITH HYPERTHYROIDISM

GEORGE CRILE, JR.

### I. GENERAL PRINCIPLES

PATIENTS with hyperthyroidism are nervous and over-reactive to stimuli. Their emotional tension is so great that it can be released by the slightest provocation into an outburst which may go on to a thyroid crisis. There is probably no other condition in which changes induced by trivial procedures can develop so rapidly into critical states that threaten life. For these reasons, the patient with hyperthyroidism must be managed with extraordinary care. The complications of hyperthyroidism (thyroid crisis, cardiac decompensation, etc.) which are so difficult to treat are, in the majority of cases, relatively easy to avoid. We must, therefore, anticipate the complications that are likely to arise and treat them prophylactically before they develop.

### II. ROUTINE PREOPERATIVE CARE

1. **Physical and Mental Rest.**—The patient should be hospitalized so that she will become thoroughly accustomed to the hospital environment. She should not be allowed visitors other than members of the family; the length of the visits should be limited to fifteen minutes; there should never be more than 2 visitors present at a time; and the visitors should be asked to refrain from discussing any subject which might disturb the patient. She should not be in a room with patients who are recuperating from operations, and the nurses and doctors should not discuss the coming operation with the patient except in a reassuring way. The patient should never be notified when the operation is to be performed. When the

200 kv. and heavy filtration, giving an effective wavelength of about 0.15 angstrom or shorter.

The skin-tolerance dose is considered to be 800 roentgens when back-scattering is included, if the dose is given in one sitting. However, in the past few years we have administered four or five times this amount to each field by daily applications of from 200 to 300 roentgens and have secured much better results.

The fields are planned to crossfire anteriorly and posteriorly the thyroid area, the supraclavicular region and the upper mediastinum regardless of whether or not the growth is considered to be bilateral or to have extended substernally. The roentgen beam is directed to the midline from each portal and includes the trachea and thyroid isthmus, which should receive a therapeutic dose on account of the probability of neoplastic invasion. Inflammation within the trachea may ensue at the height of the irradiation reaction, but usually can be relieved by intratracheal injections of oil, although in some patients who have had extensive invasion necessitating large doses of radiation, a tracheotomy may be necessary. Ulceration in the trachea has been produced in a few instances, but this has not been a serious complication, and the temporary discomfort is better than death from the disease.

although occasionally improvement may be noted even after the third week. By this time, even those patients who enter on the verge of crisis are taking food and fluids well and are mentally clear. When the pulse curve has fallen nearly to the base line, when the weight curve shows a consistent rise, and when the clinical appearance of the patient indicates that she has developed as much emotional stability as can be expected, then the time for operation has arrived. Even if the basal metabolic rate is high, the patient is in as good a condition for operation as she will ever be.

### III. POSTOPERATIVE TREATMENT

1. **Fluids.**—Following thyroidectomy, the patient is often reluctant to take fluids by mouth. Therefore, an infusion of 2000 cc. of normal saline solution should be given to make up for the fluid lost during the operation and to balance the losses of water through the skin, which as Coller<sup>3</sup> has shown, are so great in patients with hyperthyroidism.

In patients with severe hyperthyroidism, it is advisable to give a 5 or 10 per cent solution of glucose in normal saline intravenously. The fluid intake, except perhaps in patients with cardiac decompensation, should be between 3000 and 4000 cc. daily. In order to preserve and replenish the glycogen reserves of the liver in patients who are not taking nourishment by mouth, it is well to give at least 150 Gm. of glucose intravenously along with the fluids. Three thousand cc. of 5 per cent glucose in normal saline given by means of the continuous intravenous drip is the minimum postoperative fluid and carbohydrate requirement of the patient with severe hyperthyroidism who is taking little or nothing by mouth. In the average case, however, fluids are taken well after the first day, and a hypodermoclysis immediately following operation will suffice.

2. **Transfusion.**—A blood transfusion given immediately after operation is valuable in patients with severe hyperthyroidism or in aged or debilitated patients. The time to start the administration of parenteral fluids, and the time to

patient knows that the contemplated operation will occur the next day, a night of worry will often ensue and the pulse may be elevated 20 or 30 points in the morning. Absolute bed rest without getting up for bathroom privileges or for any other purpose should be insisted upon. In short, the preoperative hospital stay should be a phase of complete mental and physical rest.

2. **Sedation.**—Sedatives are valuable during the preoperative period, and experience has shown us that bromides are of more value than barbiturates in patients with hyperthyroidism. Occasionally, especially in older patients or in cases of extreme hyperthyroidism, barbiturates will excite the patient or may even precipitate a maniacal state. Thirty grains of sodium bromide twice daily is usually enough to dull the edge of the overactive emotional response. If the patient is delirious, additional sedation may be necessary, and morphine is usually the most effective drug to use.

3. **Diet.**—The diet should be of high caloric content in order to balance the increased demands of hypermetabolism. It is important, especially in cases in which edema is present and in which the serum proteins are low (as is often the case in severe hyperthyroidism), to give large amounts of proteins.<sup>1</sup> Preoperative blood transfusions are of definite value in raising the serum proteins in extreme cases where extensive edema is present.

4. **Iodine.**—Iodine, as shown by Plummer<sup>2</sup> exerts a striking effect in the control of hyperthyroidism. The administration of 1 cc. of Lugol's solution three times daily, usually in grape juice, is an effective means of administering iodine, but sodium iodide in equivalent doses is probably equally efficient. Iodine should be given preoperatively in case of hyperthyroidism associated with any type of goiter, either nodular or diffuse.

5. **Time of Operation.**—The preoperative routine is continued until the pulse curve has come down to the point where it begins to flatten out and until it does not appear that it will fall any lower. Usually, this occurs in from one to two weeks,

tion and any elevation to 102° F. or above should be reported at once to the physician. In hot weather, it is doubly important to follow the temperature closely and it is often advisable to take hourly readings because the temperature may rise with great rapidity. The importance of the temperature factor is shown by the increased incidence of fatal thyroid crises in the hot summer months, this complication in our series being 2.4 times as frequent in these months as in the remainder of the year.

In order to prevent the rise of temperature and the vicious circle of hyperthermia and hypermetabolism that characterizes a thyroid crisis, we must refrigerate the patient to the extent that we abstract more heat than can be produced. If we fail to do this, the temperature may continue to rise to 106° F. and higher, and the patient literally burns herself up in a crisis of hypermetabolism and hyperthermia.

If 10 grains of aspirin fail to reduce the temperature, refrigeration by means of ice-bags should be started. When the temperature reaches 102° F., 6 ice-bags should be applied around the lower extremities. At 103° F., ice-bags should be placed along the sides and should completely surround the lower extremities. At 104° F., a sheet is saturated in alcohol, placed over the patient, and an electric fan is allowed to play on the sheet. If this fails to control the further rise of the temperature, the patient is literally covered with cracked ice which is held in a special rubber bag large enough to cover the entire body. Care should always be taken that the skin is protected by a flannel sheet from direct contact with the cold rubber of the bag. The ice-cooled oxygen tent, as we have mentioned before, is also of value in the control of hyperthermia.

#### IV. MANAGEMENT OF THE PATIENT BETWEEN STAGES OF A DIVIDED OPERATION

In the management of patients who are sent home for three months between the stages of a divided operation, either following ligations or between lobectomies, it is important to



give a blood transfusion is not after the patient's pulse and temperature are rising into a thyroid crisis, but directly after the operation, so that the postoperative reaction will be minimized. A few hours of delay may mean the induction of a vicious circle of hyperthermia and hypermetabolism. It should be remembered that the metabolic rate rises 7.2 points with each degree of rise of temperature, and that the hypermetabolism in turn results in a greater production of heat and in a further rise of temperature. The hypermetabolism, moreover, puts an additional burden on the already overstrained myocardium, auricular fibrillation not infrequently follows, and a postoperative reaction that could have been avoided by prompt prophylactic treatment may go on to thyroid crisis, cardiac decompensation and death.

3. **Sedatives.**—It is extremely important to give sedatives, preferably morphine, in doses sufficient to keep the patient comfortable, free from worry, and at rest. The administration of sedatives should not be left to the nurse, but should be under the direct supervision of a physician. The nurse will often hesitate to give morphine frequently enough to control restlessness; the patient will become anxious and excited; a further elevation of the temperature will result; and an additional burden will be imposed on the myocardium. For this reason, postoperative narcotics cannot be given at routine intervals, but should be given in accordance with the patient's needs.

4. **The Oxygen Tent.**—The oxygen tent is of great value in the treatment of postoperative thyroid reactions. The temperature often falls several degrees after an hour or two of its use. Whether this effect is the result of the oxygen, of the refrigerated air of the tent, or of a combination of the two factors, is not yet certain, but it is well established that the tent is of definite value. In bad risk cases, it is usually advisable to place the patient in the tent immediately after operation in order to forestall the expected reaction.

5. **Control of Hyperthermia.**—The temperature should be taken every two hours for the first two days after opera-

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#### IV. MANAGEMENT OF THE PATIENT BETWEEN STAGES OF A DIVIDED OPERATION

In the management of patients who are sent home for three months between the stages of a divided operation, either following ligations or between lobectomies, it is important to

bear in mind the possibility that if iodine medication has been administered for a long time before the patient entered the hospital, the hyperthyroidism may be partially under control and may actually be more severe than is apparent clinically. Therefore, if the patient is sent home following, for example, a ligation, and if iodine is withdrawn before the full benefits of the operation have been received, it is possible that an exacerbation of the hyperthyroidism may occur incident to the withdrawal of iodine, and that this exacerbation may be more severe than the remission induced by the ligations. If this is the case, a thyroid crisis may ensue at home, or the patient may go on to cardiac decompensation. We believe, therefore, that following the first stage of a divided operation, iodine should be administered until the remission induced by the operation is well established.

Although we believe that iodine loses its maximum effectiveness after protracted use, iodine undoubtedly does exert a partial control of hyperthyroidism for an indefinite period of time. For practical purposes, it is therefore usually safer to give patients who are not under direct observation between the stages of a divided operation small doses (2 or 3 minims) of Lugol's solution daily.

#### V. INDICATIONS OF UNFAVORABLE PROGNOSIS

The only two absolute contraindications for the surgical treatment of hyperthyroidism are persistent delirium or persistent vomiting. There are, however, certain factors whose presence, although they do not contraindicate surgery, constitute a warning of an unfavorable prognosis.

In order to determine the relative prognostic significance of the various factors which generally are considered to constitute warnings, an analysis of the fatalities which followed operations for hyperthyroidism in the years from 1924 through 1934 has been made. If these warnings are classified according to the ratio between their incidence in the group of patients who died following operation and their incidence in an equal number of patients in each year who were picked at

random from those who survived operation, it is found that cardiac complications stand first in importance. In other words, auricular fibrillation, cardiac decompensation, myocarditis or valvular heart disease occurred seven times as frequently in the patients who died after operation as in those who survived operation. Substernal goiter was present six times as often in those who died following operation; a flat pulse curve, *i. e.*, a pulse curve which did not come down in response to the preoperative treatment was present five times as frequently; and the age was over 60 in five times as many

### RELATIVE IMPORTANCE OF VARIOUS WARNINGS

Figures based on ratio of incidence of special warnings in patients who died following operation to their incidence in patients who survived operation

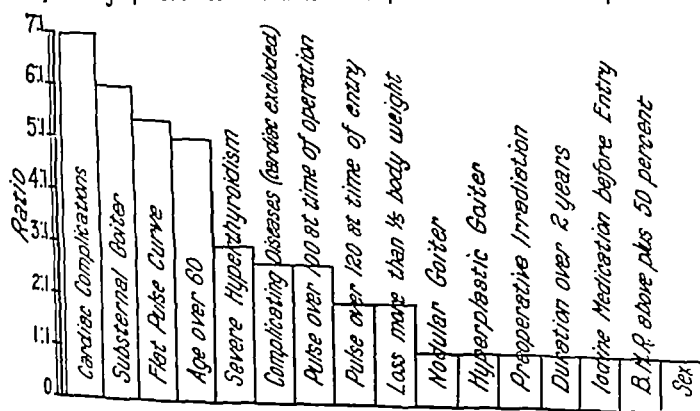


Fig. 182.

of the patients who died after operation as in those who survived. A pulse rate of over 100 at the time of operation was present 2.5:1 times as frequently in those dying after operation as in those who survived; the presence of complicating diseases, tuberculosis, diabetes, etc., but not including cardiac disorders, was in a ratio of 2.5:1 in the dead as compared to the living. A pulse rate of over 120 at entry was present in a 2:1 ratio; as was also loss of more than one fifth the body weight. An analysis of all other factors, such as the presence of nodular goiter, of a hyperplastic goiter, of pre-

operative irradiation, of duration of the disease for more than two years, of a history of iodine medication before entry, of a basal metabolic rate above plus 50 per cent, showed that each occurred as frequently in the patients who survived operation as in those who died following operation (Fig. 182).

We conclude, therefore, that the association with hyperthyroidism of cardiac complications, of a substernal goiter, of a poor preoperative response of the pulse curve, or of old age, indicates that the operative risk is increased. The mere severity of the hyperthyroidism as indicated by loss of weight or a high basal metabolic rate, however, does not imply an increased operative risk if the above complications are not present.

#### VI. THE PREVENTION OF POSTOPERATIVE COMPLICATIONS

Analysis of the cases which have terminated fatally following thyroidectomy shows that in those patients who have a flat pulse curve (*i. e.*, a pulse curve which does not come down in response to the preoperative treatment), in those who have a basal metabolic rate of more than plus 50 per cent, and in those who have a psychosis or clinical evidences of severe hyperthyroidism as judged by the patient's behavior, postoperative thyroid crisis is the commonest cause of death (Fig. 183). In substernal goiter in patients with preoperative pulmonary complications and in old age, the greatest risk is pneumonia (Fig. 184). Myocardial failure is the most frequent cause of death in patients with auricular fibrillation, cardiac decompensation or evidences of chronic myocardial damage and also in those patients in whom hyperthyroidism has been present for more than two years (Fig. 185).

**1. The Prevention of Thyroid Crisis.**—In the first group—*i. e.*, in those patients who have an excessively high basal metabolic rate, a flat pulse curve, or in those who have a psychosis—all therapeutic measures against thyroid crisis including blood transfusion, parenteral fluids, intravenous glucose, the oxygen tent, and morphine in doses sufficient to insure comfort and rest, should be used immediately following

## Causes of Death

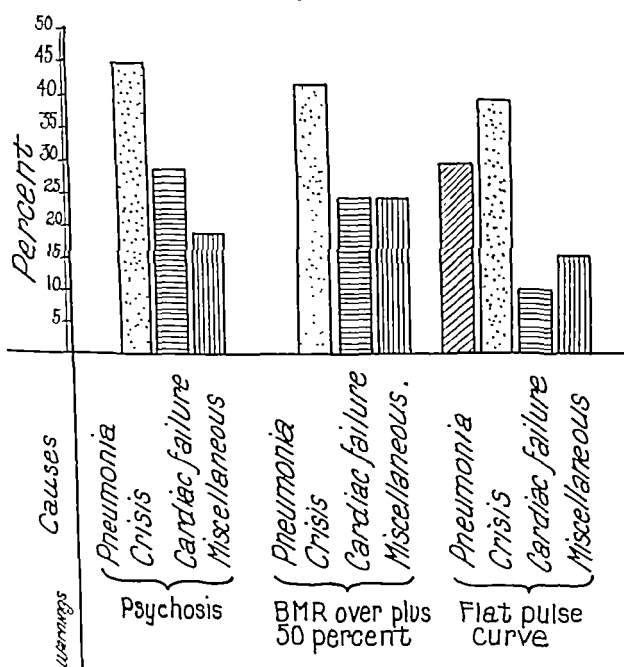


Fig. 183.

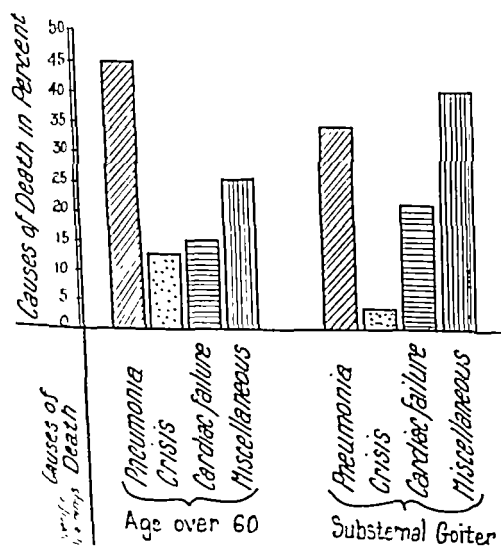


Fig. 184.

the operation and every effort should be made to control the temperature by means of antipyretics and refrigeration.

While we believe that small amounts of iodine should always be continued after operation, we never have felt that the postoperative use of large doses of iodine exerted any striking effect on the thyroid reaction of a patient who before operation had received the maximum amount of iodine. We

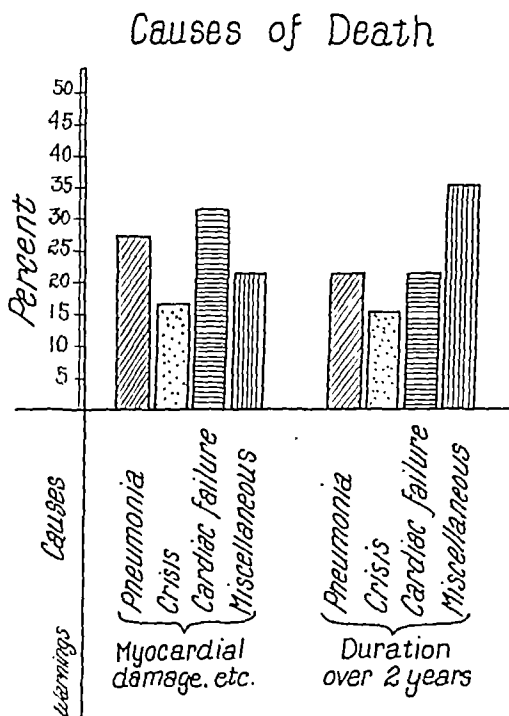


Fig. 185.

have shown in the experimental laboratory that the administration of iodine exerts no effect on the elevated metabolism of completely thyroidectomized dogs fed on large quantities of desiccated thyroid. The effect of iodine is, therefore, not on the tissues of the body or on the thyroid hormone circulating in the blood, but its action is rather a direct one on the secretory activity of the thyroid gland. For this reason, large doses of iodine cannot be expected to cause any

effect on the postoperative reaction of a fully iodized patient. The best we can do is to carry on with the routine small dose of iodine so that at least there will be no exacerbation of symptoms incident to its withdrawal.

If the surgeon believes that the patient's greatest hazard is from the severity of the hyperthyroidism and if the patient is relatively young and otherwise in good condition, a basal anesthesia of avertin is of definite value in calming the patient and minimizing the postoperative reaction. If, however, the patient is old or debilitated, the use of this drug is contra-indicated as will be explained later.

**2. The Prevention of Pneumonia.**—The management of the aged patient, in whom pneumonia is the greatest hazard, is quite different. We have seen that sedation and avoidance of psychic disturbances are fundamental principles in the management of severe hyperthyroidism in the young adult. But in the aged, we must not depress the respiration or the internal metabolism of the body because of the danger of inducing a terminal pneumonia. Depressant drugs are tolerated well in the young but easily force the aged below the critical threshold at which resistance cannot overcome the ever-present tendency to pneumonia. Every resource at our disposal must be utilized to build up the resistance of the aged patient and stimulate the vital functions. Preoperative and postoperative blood transfusions are of especial value in the aged, and there can be no question as to their efficacy in increasing the patient's resistance and strength.

As we have shown already, the chief hazard in the aged is pneumonia, while death from thyroid crisis is relatively rare. Hence, in the aged, it is better to perform the operation under local anesthesia with a minimum of gas oxygen analgesia. Avertin or any general anesthesia with its secondary depression of respiration, the cough reflex, and of intracellular metabolism should be avoided even at the expense of an occasional mild psychic reaction.

In old age, the principle of the multiple stage operation should be followed, and a lobectomy should be performed if



there is any question in the mind of the surgeon in regard to the ability of the patient to withstand a more radical procedure. Pneumonia may follow even a relatively mild post-operative reaction, and the general condition of the patient as well as her status in regard to hyperthyroidism should be given prime consideration in the choice of both the time and type of operation.

The use of the oxygen tent has lessened the mortality rate from pneumonia. The aged patient with hyperthyroidism therefore should have oxygen therapy at least as soon as any signs of pulmonary congestion occur. In addition, we believe that the severity of the thyroid reaction has been reduced by the use of the oxygen tent, and that bad-risk patients of all ages make better progress when oxygen therapy is started immediately after the operation.

In the aged, ice packs should be applied only when absolutely necessary, so that chilling with its attendant liability to pulmonary complications may be avoided.

**3. Prevention of Myocardial Failure.**—Preoperative digitalization should be reserved for those patients who have auricular fibrillation or cardiac decompensation. As soon as either of the latter two complications are discovered, the patient should receive digitalis immediately. Oxygen therapy is of value in these cardiac complications as is morphine in doses adequate to insure rest. In this way, the failing myocardium is strengthened by the digitalis, the efficiency of the oxygen-distributing function of the heart and blood is increased by the oxygen tent, and the metabolic demands of the organism as a whole are decreased by the morphine to the point where a balance between oxygen supply and demand is struck and cardiac compensation is restored. Blood transfusion is contraindicated in the presence of acute cardiac decompensation, and parenteral fluids should be limited and given very slowly.

Auricular fibrillation should be treated by digitalis until the postoperative reaction has subsided. Although the administration of quinidine will then usually restore a normal

rhythm, it must be remembered that this is dangerous in cases in which the fibrillation is of long duration and in which there is a possibility that an auricular thrombus may be dislodged when the heart reverts to normal rhythm.

### CONCLUSIONS

1. It is easier to avoid the complications that follow thyroidectomy than it is to control them after they have developed.

2. In patients with pulse curves that do not respond to the preoperative routine, in patients with excessively high basal metabolic rates, and in patients who have marked emotional instability or a preoperative psychosis, the greatest danger is from thyroid crisis and specific measures for its prevention should be taken early.

3. In patients with substernal goiter, in patients with preoperative pulmonary or upper respiratory disease, and in the aged, pneumonia is the greatest risk and every means for its prevention should be used.

4. In patients with long-standing hyperthyroidism and in patients with auricular fibrillation, cardiac decompensation or myocardial damage, cardiac failure is the greatest hazard, and specific treatment should be directed to sustain the weakened myocardium.

5. The presence of cardiac complications of old age, or of a substernal goiter increases the operative risk of patients with hyperthyroidism but a history of loss of considerable weight, or the finding of a high basal metabolic rate does not increase the operative risk unless other complications are present.

6. If the weight curve rises and the pulse curve falls satisfactorily in response to the preoperative routine, the post-operative course is usually smooth.

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## DIAGNOSIS AND TREATMENT OF NOCTURNAL INDIGESTION

C. L. HARTSOCK

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THE bedside telephone awakens the tired practicing physician to announce that Mr. or Mrs. Brown or son Johnny is having an attack of severe indigestion. Will the doctor come over immediately because Johnny has been sick all day and they were sure he was going to be better by night but instead the pains are worse; or, "Please hurry, doctor, Mrs. Brown is having indigestion with so much gas she can't get her breath and thinks she is dying"; or Mrs. Brown urges haste because Mr. Brown went to bed not feeling very well and wakened up with an excruciating pain in his stomach and shoulders which won't clear up. Even the incandescent bulb, telephone and automobile have failed to dispel the terrors of the darkness and the conscientious physician knows that he must go. Johnny may have acute appendicitis which will rupture before morning. Mrs. Brown is probably only hysterical but she will not be better until she is reassured. Mr. Brown may have a coronary occlusion or the pain may be caused by gallstones or perforation of an ulcer and the diagnosis must be made accurately and quickly. Delay may mean serious consequences.

The frequency with which such dramatic episodes occur and the knowledge that the arts and resources of the physician are taxed to the limit on these occasions make it necessary that we keep in mind those diseases which may cause nocturnal indigestion as well as safe and adequate therapeutic measures for their relief. Obviously, any form of digestive disturbance can occur at night as well as during the day, but

the purpose of this article is to emphasize briefly certain common diseases of the digestive tract or those which simulate diseases of the digestive tract that are particularly prone to occur during the night.

Indigestion which occurs at night can conveniently be classified in two groups:

1. Those digestive upsets which occur fairly regularly at night but also manifest similar symptoms during the day, and are the result of chronic disease of the gastro-intestinal tract.
2. All those conditions which occur in an acute form at infrequent intervals and often without any previous warning of ill health.

The physician is rarely called at night to prescribe for patients whose symptoms are in the first group because these are not severe. The patient has usually suffered in a similar manner during the day and knows how to relieve the distress or he is not so frightened but that he is content to wait to consult his physician at a more opportune time.

**Ulcer.**—The best example of this type of indigestion is the characteristic burning, gnawing pain of duodenal and sometimes of gastric ulcer. During the day the pain usually comes on from two to four hours after meals, but frequently at night the pain is delayed until six or eight hours after eating and the patient is wakened between 12 and 2 o'clock in the morning. The same distress is recognized which has been present during the day and relief can usually be secured by eating some crackers which the patient frequently keeps by the bedside or by drinking some milk or taking some alkaline powder. When mild obstruction of the pylorus is present, the stomach gradually becomes overloaded with the accumulated intake of the whole day's diet and the patient must vomit to secure relief. At times, there is no food retention but there is marked hypersecretion so that large quantities of liquid material are eructed and this is commonly called water brash.

Occasionally and more particularly in older patients, the only symptoms of ulcer are those which occur at night. A history of nocturnal pain occurring regularly every night for

several weeks at a time, followed by an interval of relief furnish the most reliable evidence that an ulcer exists. Nocturnal pain of this type usually indicates a more penetrating type of ulcer and one in which the management of the ulcer should be especially well regulated to prevent perforation. When the usual treatment of frequent feeding and the use of alkalines is employed, it is continued only until 8 or 9 o'clock in the evening and this gives an opportunity for the acid to accumulate and cause pain at a later hour. Often sodium bicarbonate or other alkalies which cause a secondary secretion of acid are used in the treatment and when they are discontinued at bedtime, the secretion of acid is even higher than usual, thereby causing the night pain.

When night pain occurs in the presence of an ulcer, this is more difficult to relieve than the periodic postprandial distress that occurs during the day. If it is not relieved by the usual treatment, alkalies and feedings should be continued until a later hour or they can be given during the night if the patient wakes with distress. Preferably, the alkalies should be of the slow neutralizing type such as calcium carbonate, which also has the advantage of not stimulating a secondary rise of acid. Calcium tribasic phosphate is also very good for this reason. I have found that a colloidal suspension of aluminum hydroxide is especially helpful for night pain because it has such a long period of neutralization. A teaspoonful in a full glass of milk at bedtime will control the pain in most of these cases. The patients who have obstruction which is thought to be due to edema and spasm and which will frequently respond to medical management should have nightly gastric lavage until the obstruction is relieved. Sedatives and atropine are also helpful. As long as the nocturnal pain of ulcer resists treatment, it means that the ulcer is in a very active state, no matter how well the patient may feel otherwise.

**Spastic Colon.**—Another common cause for night pain is found in the spastic, irritable colon. This is manifested by distress low in the abdomen and sometimes by mild or

severe cramps which awake the patient about 5 o'clock in the morning, or are present when he wakes at his usual hour and these persist until the morning meal. A bowel movement sometimes will relieve and sometimes aggravate the pain. The passing of flatus gives relief and this fact is of diagnostic importance. The treatment of this condition is the usual treatment for irritable colon, that is, rest, smooth diet, heat, sedatives, natural regulation of the bowels and the avoidance of laxatives and large enemas. Allergy should be considered as an etiological factor.

Hyperacidity which is due either to nervous excitation or reflex excitation from a chronic appendix or diseased gall-bladder will cause night distress at occasional times but not with the regularity of an ulcer or irritable bowel.

The regularity of occurrence and the time of occurrence at night are valuable diagnostic aids in differentiating these three conditions—ulcer, reflex hyperacidity, and spastic colon, if more precise *x-ray* investigation cannot be employed.

**Hydronephrosis.**—Hydronephrosis with symptoms referred to the gastro-intestinal tract frequently gives night pain simulating digestive disease and which is due to overdistention of the bladder and renal pelvis. The history of relief after urination is a valuable diagnostic clue.

**Hypertrophic Arthritis.**—The pain which occurs in the low back region early in the morning and which is due to hypertrophic arthritis is frequently referred to the lower abdominal area and the patient is misled into believing that he has a gastro-intestinal disorder. This type of distress can usually be distinguished by its relation to a back pain and also because it disappears shortly after the patient gets up and begins to move about.

**Diarrhea.**—Diarrhea which lasts more than a few days and occurs at night usually is of organic rather than functional etiology. Morning diarrhea and postprandial urgency without nocturnal diarrhea are more often due to functional causes.

**Causes in Children.**—Children are apt to have periods

excitation and fatigue, dietary indiscretions or allergic sensitization to foods.

The emergencies of the night, as those cases included in Group 2 might be called, place a tremendous responsibility on the physician who is called to render aid. The diagnosis must be made quickly and accurately and under adverse circumstances of excitement, fear, and limited facilities. Immediate relief of pain is demanded by the patient and relatives, although from the physician's standpoint, the relief by morphine often means masking the symptoms and consequently the correct diagnosis. Decisions based upon flimsy evidence and hasty observation must be made with confidence when the physician knows that the life of the patient may depend upon this decision.

The important problems facing the physician in these emergencies are to relieve the patient without endangering his future chances of recovery, to decide on the advisability or inadvisability of surgical intervention, to suggest a consultant if deemed advisable, to plan a course of therapy and observation when the acute emergency has passed and lastly, to allay the fears and anxieties of the patient and his relatives.

The acute conditions which might be called indigestion are so numerous that it obviously is impossible to describe them in detail and many will even escape mention. Such conditions as perforated ulcer, acute pancreatitis, acute appendicitis, intestinal obstruction, strangulated hernia, ovarian cyst with twisted pedicle, ruptured ectopic pregnancy, etc., are mentioned only to point out that the symptoms and signs should cause them to be recognized as acute surgical conditions, the correct diagnosis often being in doubt until after the exploration. The constant demand by our surgical colleagues for the early recognition and exploration of the acute abdomen makes it unnecessary to discuss these problems here. Certain other conditions which occur more frequently and are typical of acute nocturnal indigestion will be discussed more fully.

Gallstones.—The gallstone has a habit of wandering into



the cystic duct during the early hours of the morning. The typical attack is easy to diagnose, but at times the first attack may be more baffling. No matter how atypical the attack, the signs and symptoms rarely suggest the acute surgical abdomen, and it is usually advisable and safe to administer a hypodermic of morphine in a liberal amount. If relief is not obtained by at least the second dose of morphine, one should begin to question the nature of the trouble. Even when gallstones are known to be present, serious complications should be suspected if relief is not prompt following an adequate amount of morphine. It has been my observation that many physicians are prone to try simpler remedies in an endeavor to relieve the attack without resorting to morphine. If the diagnosis seems reasonably certain, there is no sound reason for withholding morphine. The relief is prompt, the stone is passed and there is much less chance for the development of complications.

**Coronary Occlusion.**—A condition that must constantly be kept in mind when the physician is called at night, especially if the patient is a man past forty years of age, is coronary occlusion. Patients almost always consider this as acute indigestion, but this condition demands more than the average diagnostic acumen to differentiate it from some of the upper abdominal emergencies. The onset is frequently associated with mild digestive symptoms during the day and early evening which culminate in the severe attack during the night. The frequent occurrence of these symptoms in the male, the prostration, character, location and distribution of the pain, the fall in blood pressure and at times, a friction rub should serve to clarify the diagnosis in the great majority of cases. However, mild attacks are the most confusing. This is unfortunate because if these attacks could be recognized early and proper therapy established immediately, the lives of many men just reaching their prime could be prolonged for several more useful years at least.

Absolute rest and plenty of morphine to relieve the pain is imperative at the time of the attack. The subsequent treatment can be found in any discussion of coronary occlusion.

There is one type of indigestion which occurs almost exclusively at night, but so far as I know, has never been given a satisfactory name although it is a definite clinical entity and is responsible for a large percentage of the emergency calls at night. The usual telephone message is to come at once, someone is dying. If the doctor has had a previous experience with the same patient, he need not be in such a great hurry. The story is practically the same in every case. The patient, usually a woman of any age, is awakened with a great pressure around her heart. She is unable to get her breath, the heart is racing wildly, the hands and feet are numb and there is a sensation and fear of impending death. Shortly after the physician arrives, examines the patient and gives a few words of reassurance, there is a remarkable improvement. If the physician is of the type that inspires confidence, the attack is soon over. The day preceding this attack has usually been an exciting, fatiguing one for the patient, and the attack is a combination of nervous indigestion, hysteria and panic. If the physician who is called to attend such a patient does not wish to have his rest interrupted frequently, he should take measures to prevent similar episodes, which usually become quite regular after the first attack. A spastic colon is usually the cause of these attacks. The spasm of the descending colon causes a gaseous distention of the splenic flexure and the vagus and sympathetic nerves of the heart and respiration probably are stimulated by reflex action. Treatment for a spastic, irritable bowel should be instituted with smooth diet, rest and heat to the abdomen after meals, especially the evening one, the establishment of regular bowel elimination without the use of laxatives and enemas and the use of a mild sedative and belladonna or atropine in some form.

If, in her first few attacks, the patient has been so unfortunate as to secure the services of a physician of the alarmist type, fear often becomes so deeply rooted that in spite of the best treatment, the patient may become a semi-invalid for the rest of her life. Therefore, it is most important for the physician to inspire confidence in the patient and thus relieve

her fear. If the patient does not respond to this psychotherapy in her first attack, the symptoms generally will subside promptly after the use of heat and massage to the extremities, or a warm bath. A quick-acting sedative will usually induce sleep and the doctor may go home not impatient at being called out because of an hysterical woman, but rather with the feeling that, if he has handled the situation well, he may have been responsible for preventing invalidism just as completely as though the attack had been due to some organic disease.

**Ptomaine Poisoning.**—Severe abdominal cramps accompanied by diarrhea are often the presenting symptoms that demand a night call. The presence of diarrhea is a fairly reliable clue that the lesion will not require surgical intervention. In the presence of severe ptomaine poisoning, the patient may, however, become quite rapidly dehydrated so that severe prostration results and at times urgent treatment is required. The temperature may fall rapidly to a very low figure so that much artificial warmth is essential. Infusions of glucose and saline may be necessary. I have never felt that the time-honored castor oil therapy was a logical or safe treatment even in the mild cases. Complete starvation and opium sedation has always given quicker and better results in my experience.

**Renal Colic.**—Renal colic should only be mentioned in a discussion of nocturnal indigestion because it often simulates disease of the digestive tract and when it occurs on the right side, it is especially hard to differentiate from acute appendicitis. In cases where differentiation is difficult it is important to make a microscopical study of the urine before a too hasty operation is advised.

With this brief review of a few of the many possible causes of acute nocturnal indigestion, we may simplify the subject somewhat if we approach these difficult problems by trying to place the cases in one of the following groups:

**Group I.**—Those patients who can be given complete relief from symptoms quickly and at the moment, until a more

accurate diagnosis can be made at a time far before the onset of this group are those with such diseases as gallstones, biliary colic, pylorospasm.

**Group II.**—Those patients to whom it is difficult to give immediate relief and treatment of symptoms is difficult. It requires very close and possibly constant observation during the entire duration of the illness. Coronary thrombosis, severe lead poisoning, massive hemorrhages from the gastro-intestinal tract, suspected poisoning fall in this group.

**Group III.**—Those patients in whom there is great possibility of an acute surgical abdomen. These patients should be hospitalized immediately and temporary relief given only if absolutely necessary so that the symptoms may not be masked. Further diagnostic measures such as examination of the blood and urine and a plain roentgenogram of the abdomen should be made immediately on arrival at the hospital. A flat plate of the abdomen gives invaluable information in such conditions as perforated ulcer and intestinal obstruction.

**Group IV.**—Those patients whose symptoms are due to purely functional causes, but to whom the physician should give a great deal of attention during the attack in order to avoid implanting further fears. When such a condition is suspected, the examination should be more careful than usual, which in itself is very calming to the patient, and it is also advisable to follow this examination by a more detailed study at the earliest convenience. Such procedures frequently will cut short what may prove to be a long, distressing episode in the patient's life and a source of considerable worry in the doctor's life.

**Group V.**—Those patients in whom the symptoms are too indefinite to classify into any one of the above groups but who can be safely but closely watched until the diagnosis is more clearly established. Personally, I prefer to hospitalize these patients but frequently this is difficult and many factors must be taken into consideration, not the least of which is the close attention the physician is able to devote to observation of the patient.

In conclusion, a simple classification of nocturnal indigestion has been suggested in which two distinct groups are pointed out, and in the latter group, which calls for the most accurate and difficult decisions a doctor has to make, five further subdivisions have been made. Certain therapeutic principles have been discussed.

This classification, even though it is based upon the most indefinite, pathological and diagnostic criteria, has helped me approach these problems with greater ease, less worry, and better results to the patient.

## THE TREATMENT OF SPLANCHNOPTOSIS

JOHN TUCKER

### GENERAL CONSIDERATIONS

As a general rule, those people who have inherited the tall spare conformation of the body possess abdominal organs that lie below the normal position. However, the circulation may or may not be disturbed by symptoms of ill health, although very frequently such anatomical variations are accompanied by lack of ability to withstand a prolonged period of stress and strain, whether it be mental or physical. When a severe illness is experienced, a childbirth or a period of unusual worry in business or in the home, many symptoms appear which may lead to a greater or a lesser degree of invalidism.

### CLASSIFICATION

The congenital form with which we are chiefly concerned in this discussion is divided by Cawadias<sup>1</sup> into four distinct groups:

(a) The syndrome designated by Stiller as the constitutional type. Other writers have described it as the linear type, the microsplanchnic or hypovegetative constitution. In these patients the thorax is usually longer than the abdomen, it is narrow in width and shallow in the antero-posterior diameter. The subcostal angle is acute, the heart is vertical and the diaphragm is low, all of which conditions produce diminished capacity in the upper abdomen. Other mechanical features which contribute to splachnoptosis will be considered later. In many instances the ptosis does not affect all the abdominal organs to an equal degree. There may be gastropptosis, with or without ptosis of the duodenum. Likewise, nephropptosis may be accompanied by ptosis of the right colon, or on the

other hand, the major symptoms of distress may be caused by a general coloptosis.

The symptoms may vary in different patients, but the majority are disturbed by dyspepsia, constipation and nervous instability. Various other symptoms such as menstrual irregularities, low blood pressure, and chronic fatigue with hypometabolism may suggest an endocrine factor in the etiology. Many patients show allergic sensitivity and low resistance to infections, especially of the respiratory tract. This picture is familiar to all physicians who are in clinical practice.

(b) A second group is described by Adler<sup>2</sup> in which the anatomical features of splanchnoptosis are accompanied by symptoms of excessive nervousness. There are frequent headaches, brooding and depression even to the point of melancholia. The appetite is capricious, the bowels are habitually constipated and the "cathartic habit" is well established. The constitutional inferiority of these patients is evident in early childhood. They are the prima donnas of their family. They must be spared any worry or shock, and the household activities are modified according to their wishes, thereby establishing a vicious circle, which may lead to neurasthenia or chronic invalidism. It is much easier to obtain satisfactory therapeutic results if these patients can be studied and treated before the period of puberty is over.

(c) The third type or Glénard's disease is characterized by a more severe form of visceral displacement. In this form there may be symptoms such as are seen in Dietl's crisis, pylorospasm, and duodenal stasis. The common symptoms are headache, vomiting, anorexia or severe abdominal colic. In the presence of severe coloptosis, there may be obstinate constipation or symptoms suggestive of chronic appendicitis. It is usual for such symptoms to disappear when the patient lies down in a horizontal position.

(d) A fourth type is described as organic gastro-enteroptosis in which perivisceritis with multiple adhesions occurs. This condition may follow a surgical operation or simple

colitis. The symptoms consist of more severe abdominal pain and there are greater digestive disturbances which are relieved by lying down. The acquired form of splanchnoptosis which may follow a wasting illness, or which may result from pregnancy, the removal of ascitic fluid, a large abdominal cyst or a tumor is probably of this type.

Before we can discuss the treatment of splanchnoptosis with any degree of intelligence, we must have a clear understanding of the anatomical or mechanical features which maintain the abdominal organs in their normal position. We believe that the following are the most important factors:

1. Adequate capacity of the upper abdomen. The abdominal organs cannot remain high unless there is sufficient space. In a normal person the cavity resembles an inverted pear with the larger end uppermost. The subcostal angle is wide, the sternum forward and the diaphragm relatively high.
2. Negative intrathoracic pressure of a sufficient degree so as to exert a pull on the diaphragm when it is relaxed as in expiration.
3. A strong pelvic floor to support the viscera.
4. Strong abdominal musculature with sufficient tone to withstand the inspiratory downward push of the diaphragm, and to lend normal support to the viscera even when filled with food.
5. Retroperitoneal or perirenal fat of sufficient quantity to serve as a support and proper resting place for the various organs. In addition to this, the omentum should possess plenty of fat.
6. Firm and strong attachment between the organs and the diaphragm and the posterior abdominal wall.
7. A proper body posture which is erect and without either lumbar lordosis or dorsal kyphosis.

#### TREATMENT

Satisfactory results in the treatment of splanchnoptosis cannot be attained unless the physician is really interested in the problem and unless the patient is willing to modify his



habits of living to conform with the therapeutic principles outlined below. Contrary to the opinion of many authors, we believe that the patient should be given a careful and intelligent explanation of his problem. If this is followed by adequate treatment, the results are generally satisfactory. Some of the important therapeutic measures will be discussed in detail.

1. **Diet.**—Disturbed digestion is a most common complaint of patients who have splanchnoptosis. These symptoms may consist of anorexia, heartburn, heaviness in the stomach, vague aches and pains within the abdomen or postprandial vomiting. As a rule, the emesis brings only a small part of the meal. In a few instances, gastro-intestinal hypermotility causes excessive hunger. This vagotonic syndrome can be determined in part by roentgen studies of the gastro-intestinal tract. Not infrequently we find cardiospasm, pylorospasm or a spastic descending and sigmoid colon. In such cases, relief may be obtained by the administration of from 10 to 12 drops of tincture of belladonna one-half hour before meals. The patient's tolerance to this drug will determine whether the amount should be increased or diminished. If the Ewald test meal shows a high free acidity, we may prescribe an alkaline powder, such as equal parts of calcium carbonate, bismuth subcarbonate and the heavy oxide of magnesia, which is given in doses of  $\frac{1}{2}$  teaspoonful in water one-half hour after meals. If the acidity is low, and this frequently happens, we give  $\frac{1}{2}$  teaspoonful of dilute hydrochloric acid in a glass of buttermilk or fruit juice with meals. In a few cases, food allergy can be demonstrated by skin tests or by the study of a food diary, the latter being kept by the patient. He lists the foods which are eaten at each meal and also records the time at which distress occurs. When these lists are studied with care, an offending food may be found such as wheat, milk, eggs or some less common article of the diet.

When undernutrition seems to be responsible for the trouble, we prescribe a well-diversified diet, which is high in vitamins and calories. This includes meat at least once a day, one

or two cooked eggs, milk, cream and butter, one fresh and one cooked vegetable (one of which is green—iron—and the other yellow—provitamin A), fresh and cooked fruits as desired, soups, cereals, breads, nuts and simple desserts. If the colon is spastic, excessive roughage is not desirable and therefore corn, bran, tough vegetable fiber and foods containing seeds are omitted. Milk or cream is taken midway between meals provided it does not destroy the appetite for the next meal. Light wines and beer are usually tolerated well and may serve as appetizers. Many foods should be avoided, and especially is this true of twice-cooked meats and food cooked in deep fat, pickles, olives, highly spiced food, sausages and cold meats, and canapés. Weak coffee or tea taken in moderation rarely causes distress.

When the condition is complicated by a peptic ulcer, diabetes, food allergy or other diseases which require special diets, these must be followed of course, but, if possible, they should be planned to produce a steady gain in weight to a normal or slightly above normal figure.

In certain cases, it may be necessary to give 10 units of insulin immediately before one or more meals, usually the noon meal, in order to create an appetite for food. A bitter stomachic such as nux vomica or tincture of gentian is useful in some patients. The meals should be eaten slowly, in a pleasant environment and with a pleasant companion or with music if desired. It is interesting to observe how much these well-known procedures may contribute to good digestion. If the patient is overtired, a rest of one-half hour before eating increases the appetite. Every reasonable measure should be employed to obtain a gain in weight; otherwise, we will fail to secure satisfactory results. At first, three or four weeks may pass before an upward trend in weight begins.

**2. Vitamins.**—Even though the diet which is prescribed may contain sufficient quantities of the necessary vitamins for a normal person, it is well to give extra quantities, especially for the first few months. Many deficiency symptoms such as anemia, the smooth or atrophic tongue, spoon nails, nervous

irritability and nerve root pains occur frequently enough to justify special measures. Cod liver oil is most helpful if the patient can take it without distress; if not, then cod liver or fish oil concentrates are used as a second choice. If the oil is given, 1 tablespoonful is taken once a day or  $\frac{1}{2}$  tablespoonful morning and evening. This will supply the vitamins A and D.

Vitamin B is given in the form of wheat germ, brewer's yeast, or various extracts from rice polishings, yeast or cereal germ. Many excellent preparations of vitamin B are on the market, and proper doses of any of these can be prescribed after each meal. Adequate amounts of vitamins C and E are present in fruits and vegetables. When the body weight has reached the normal for the patient's age and height, the complementary use of vitamins can be diminished in amount or discontinued.

3. **Constipation.**—As a rule, a roentgenogram of the colon shows spasticity throughout its entire extent or more frequently, there is spasm in the descending and sigmoid colon. This will be helped by the belladonna already prescribed, but additional measures may be necessary. It is our custom to advise the following procedures which may be used entirely or in part.

(a) Two glasses of warm water on rising in the morning. A pinch of salt or lemon juice may be added if desired.

(b) Postural exercises (given below).

(c) Gentle deep massage of the abdomen beginning over the cecum and following the course of the colon. This is done before the patient leaves his bed.

(d) A glycerin suppository when the patient rises or an enema of 1 pint of warm water after breakfast. These measures are used for a few days only, and may serve to develop the habit of a daily evacuation before the day's work begins.

(e) A tablespoonful of mineral oil night and morning. This may be taken with 1 or 2 teaspoonfuls of flake agar-agar, or if one prefers, the agar-agar may be taken with or immediately after meals.

(f) When laxatives are required, we prefer from 1 to 4 teaspoonfuls of a saline such as sodium phosphate, sodium or magnesium sulphate before breakfast, once or twice a week. If the bowels are spastic, cascara or phenolphthalein should be avoided since they tend to stimulate a colon which is already hypertonic.

4. **Rest.**—Both physical rest and mental relaxation are important and essential parts of the treatment. It is rarely necessary to prescribe continuous rest, but rather it should be advised whenever fatigue is noted. At the beginning of treatment, a week of quiet rest in bed may relieve excessive fatigue and exhaustion, but it should not be continued too long, because overresting may be enervating. We advise the average patient to remain in bed for ten hours at night but to arise not later than 9 A. M. If sleep is slow in coming, a glass of warm milk or a warm bath before retiring induces quietude and peace of mind. In other cases, these measures produce wakefulness. A short period of reading in bed, if the light is good and the story simple, may soothe the nerves and calm the mind. Such a luxury should rarely be denied these patients. If a drug is needed, at least for a few nights, 30 grains of bromide and 5 grains of aspirin are usually effectual.

5. **Psychotherapy.**—The home environment of patients who suffer from the nervous manifestations of splanchnoptosis is often unfavorable. The husband and wife may be temperamentally incompatible, and most frequently this centers about sex matters. The loss of sexual libido or impotence may be brought on by endocrine dysfunction, excessive physical and nervous fatigue, painful intercourse, fear of pregnancy or many other factors. In unmarried patients, much importance must be attached to an absence of normal sexual gratification. These matters should be brought to light by a frank and kindly discussion with the single patient or in married patients, a conference with both husband and wife. One should attempt to correct any deficiency in the endocrine functions so far as is possible. We have no satisfactory solution for this problem in the unmarried young people. If the normal sex

instinct can be sublimated into other channels, especially in social work among children, there is less nervous tension and increased happiness.

Adler has described many of these nervous symptoms, and he states that the psychical conflict may express itself in organic language. The sufferer is beset by fears about himself and overanxiety about the family. He may experience continuous or intermittent headaches; he may brood over his ill health; his social activities are lessened; the diet is restricted; he loses more weight and he feels more despondent. This form of psychophysical inadequacy may have existed since childhood, or it may have appeared at puberty, marriage, the menopause or following great emotional distress.

It is impossible for us to discuss the psychotherapeutic measures which should be employed. It is our work to discover the important mental conflicts and to attempt to adjust them by wise counsel. It is not enough to tell the patient to "buck up" and pull herself together. She has known for many years that she is nervous. The family physician can often evaluate the situation much better than the psychiatrist, if the doctor will but take the time and the interest in the environmental and physical factors. The problem, at best, is most difficult.

6. **Physiotherapy.**—(a). Ultraviolet light treatments are of some value as general tonic measures. We do not urge this therapy unless it can be arranged conveniently.

(b) Sinusoidal current to the abdomen once or twice a week may give better tone to the right colon. It should be discontinued if it produces abdominal distress or fails to produce better digestion or more satisfactory bowel movements.

(c) Colonic irrigations are not advisable as a regular procedure. In a normal person, the colon is not empty, and to attempt to keep it that way interferes with absorption and motility. It is possible, also, that a series of such treatments may disturb the defenses of the mucosa against absorption of toxins and bacterial invasion. We do not decry its use in ex-

ceptional cases of obstipation but we do condemn the frequent and regular use of the so-called "high irrigations."

7. **Postural Exercises.**—This is one of the most important and valuable forms of treatment for splachnoptosis. It is effective in the majority of patients if it is carried out regularly and with the proper technic. It makes very little difference whether the patient is suffering from nephroptosis, gastroptosis, coloptosis or a descensus of all of the abdominal organs. This procedure has many advantages; it produces deeper breathing, better oxygenation of the tissues, a greater capacity for the organs in the upper abdomen; likewise, it develops the intercostal muscles and also the muscles of the diaphragm and abdominal wall.

This method of therapy has been elaborated by Goldthwait<sup>3</sup> who has demonstrated that a patient with enteroptosis nearly always has a faulty posture. A profile view of the patient will show lumbar lordosis and dorsal kyphosis. The use of exercise and proper muscle training tends to correct this deformity by flattening the lower back and by bringing the head erect and the chin back. A detailed discussion of these measures is contained in the manual of Posture Exercises prepared by the Children's Bureau of the U. S. Department of Labor, Publication No. 165. A method of procedure is as follows:

(A) In lying position, on a firm bed or on the floor.

1. Deep breathing.

(a) Raise the thorax as high as possible during inspiration.

(b) Hold the ribs in raised position and breathe by moving the diaphragm up and down.

2. Pelvis tilting: keep the abdomen down and at the same time, tilt the pelvis forward and then backward, this tends to flatten out the lumbar curve.

3. With the pelvis tilted forward, draw each leg up and down with the heel close to the bed. In this exercise the knees are flexed and extended.

4. With the pelvis tilted forward, raise the head up and down.

5. With the pelvis tilted forward, raise each leg alternately, with the knees stiff.

6. Turn to the knee-chest position on the bed and kick out with each foot as high as possible. This is done with alternate feet and tends to bring the organs forward and to the upper part of the abdomen. If this exercise is taken before retiring, the patient can then slide down and sleep on the abdomen.

7. If the patient sleeps on the back, place a folded pillow under each knee and one under the buttocks; this flattens out the lumbar curve. If he sleeps on his side, keep the knees and hips flexed.

(B) Standing position:

1. With the pelvis tilted forward, flatten the back against the wall.

2. With the back flat, walk away from the wall, raise up and down on the toes and return to the wall.

3. With the back against the wall, raise alternate legs first with the knee flexed and then with the knee straight.

4. Practice alternate stooping and standing with the back flat and the chin back.

These exercises should be repeated several times at each session and should be done morning and evening.

Abdominal belts or supports need not be used in the thin patient with splanchnoptosis if he will practice his exercises faithfully. It is very much better to develop the musculature and correct the postural defects than it is to attempt mechanical lifting and support of the viscera. In obese people with pendulous abdomens, the musculature may be so weakened that a corset or belt is necessary for support. The chief requirements of a satisfactory support is that it be comfortable and that it will exert an upward pressure. The majority of patients obtain better results without mechanical appliances. We do not believe that it is necessary to have the foot of the bed raised during sleep.

8. **Surgery.**—The chief indications for surgery are as follows:

(a) Repair of the pelvic floor when there is marked pro-cidentia.

(b) Suspension of a floating kidney when there is intermittent hydronephrosis or Dietl's crisis and when the exercises and abdominal support fail to relieve the condition.

(c) Suspension of the hepatic flexure when this is excessively low and when other measures fail to restore it to the normal position.

(d) Removal of congenital veils and bands when these interfere with normal gastro-intestinal function.

As a rule, patients who suffer from splachnoptosis fail to derive benefit from surgical operation unless it is performed to correct a definite and recognized abnormality such as those noted above. And yet, how often do we see multiple incisional scars on the abdominal wall which were made for removal of supposedly diseased appendices or for pelvic operations?

#### SUMMARY

In the modern treatment of splachnoptosis, a careful study of the patient must be made from many angles. We must consider the psychological factors, the nutrition, the musculature, and the posture. Our instructions should be explicit and if possible written out so that the treatment can be understood easily. When verbal instructions are given, the patient becomes confused. Much of a knowledge of the art and science of medicine can be used in the management of these unhappy people by giving them encouragement and sympathetic understanding.

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## INTESTINAL TOXEMIA

JOHN TUCKER

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CONSIDERABLE doubt exists in the minds of many able observers that chronic intestinal toxemia is a true clinical entity. The safeguards supplied by nature in the intestinal mucosa, lymph supply and liver appear to be quite adequate for the protection of the body against the ordinary chemical substances, the usual products of putrefaction, or the fermentation activity of intestinal bacteria. No one questions the fact that acute gastro-intestinal upsets may result from the ingestion of spoiled or contaminated foods, whether the primary reactive agents be chemical or bacterial. However, what diagnosis may one make for a rather large group of patients who are disturbed periodically or intermittently by "bilious" spells which are characterized by constipation, flatulence, physical fatigue, mental lethargy, insomnia, anorexia, furred tongue, foul taste and headache? Our colleagues of a preceding generation treated a vast number of these patients, and they were honest in their belief that these symptoms were due to intestinal absorption as the result of constipation or auto-intoxication. More recently, however, if we consult the most up-to-date and generally accepted classification of diseases,\* we will find under the general heading of "Diseases of the Intestines" the diagnostic term, "Intestinal Intoxication due to Putrefaction of Ingested Food" and again under "Disorders of Carbohydrate, Fat and Water Metabolism," the term "Intoxication. Acute Intestinal" occurs. This list of diagnoses was compiled by various committees representing the leading medical groups of this country and includes both chronic and acute intestinal toxemia.

\* Standard Classification of Nomenclature of Diseases.

It is quite apparent that the function of the intestinal tract involves a complex mechanism. Among the requirements for normal alimentary activity are a stable nervous system, normal appetite, proper food, efficient digestion, normal motility and as a rule, regular evacuation from the colon. When we attempt to determine what is wrong with the patient who has a serious disturbance of this mechanism, it is also obvious that we must not be influenced unduly by a group of symptoms, but the diagnosis must be based upon a careful study of the patient's life history including his emotional reactions and eating habits as well as the objective evidence secured by careful physical examination, roentgenograms and laboratory data. These routine investigations are essential in eliminating from the diagnosis such organic diseases as chronic cholecystitis and cholelithiasis, peptic ulcer, carcinoma, chronic appendicitis, and lesions of the central and peripheral nervous systems as well as lesions of the lungs and genito-urinary tract. Any patient who has suffered with recurring attacks of digestive upsets, whether or not they have been of the bilious type, is entitled to such an examination. Most of the mistakes in diagnoses are the result of inadequate study rather than the result of professional ignorance.

From a scientific viewpoint, we are unwilling to accept the diagnosis of chronic intestinal toxemia associated with constipation until the following questions have been answered.

1. Does experimental evidence indicate that toxic substances can be absorbed from the intestinal tract as the result of putrefaction, fermentation or constipation?

2. If toxic materials or bacteria do penetrate the "intact" intestinal mucosa, can they overwhelm the defensive mechanisms of the body?

3. Can the symptoms described as "bilious" be explained by some disturbance other than the absorption of toxic products?

Many articles pertaining to intestinal toxemia have appeared in the literature, but most of them have dealt with the clinical rather than the experimental aspects of the subject.

In recent years, however, most important evidence has come from the research laboratories. Alvarez<sup>1</sup> has reviewed the experimental work on this subject and cites the following possible sources of intestinal poisons, using the classification given by Weintraud and by Wells:

1. From constituents of the digestive secretions.
2. From the products of normal digestion.
3. From the products of putrefaction and fermentation.
4. Synthetic products of bacterial activity in the bowel.

From the available evidence, he concludes that neither the constituents of the digestive secretions nor the products of normal digestion are able to produce any recognizable toxic symptoms. Many substances which may appear during the normal course of digestion such as the amino-acids, ammonia, hydrogen sulphide, volatile fatty acids, acetone or oxalic acid may play some part in temporary gastro-intestinal upsets such as diarrhea, yet they fail to give rise to any general symptoms of toxicity. A possible exception exists in the factor of food allergy, which will be discussed later.

Many chemical substances may form in the bowel from the putrefaction of proteins. These include indol, skatol, indol acetic acid, phenols, cresols, histamine, tyramine, choline and methylguanidine. In all instances, the evidence would appear to show that insufficient quantities of these toxins can penetrate the intact bowel wall or escape the detoxifying action of a normal liver to produce general symptoms. However, we have been taught for several generations that the amount of indican in the urine is a measure of the degree of intestinal putrefaction. In regard to this, Alvarez makes the following statement: "As Hale White says, there is no doubt that an excess of indican is often associated with serious intestinal disturbances and with conditions suggesting auto-intoxication, but we know also that many people pass large amounts of indican for years and yet remain in good health. Furthermore, large numbers of constipated people show no increase in the indican in their urine.

"We see then from all this, that although indol has toxic

properties and although it can produce in man some symptoms similar to those observed in the constipated, it must not be forgotten that some of those symptoms do not correspond to those observed clinically; and what is more important, experiments have been done with doses enormously greater than those met with even in the presence of disease." Pertaining to this point, there is another observation that even though feces normally contain 60 mg. of indol per 100 Gm. of fresh material, it appears evident that little of this is absorbed since only 6 to 20 mg. are excreted in the urine in the form of indican.<sup>2</sup>

In a similar manner, we can dispose of pressor substances, tyramine and iso-amylamine, which are assumed to exert some influence in the maintenance of high blood pressure. Likewise, in the case of histamine which has a depressor effect and tends to lower blood pressure, the absorption is too little to tax the detoxifying function of the liver.

The fourth hypothetical source of intestinal toxins exists in the products of bacterial activity within the bowel. It has been stated that approximately 46 per cent of the total nitrogen of feces comes from bacteria.<sup>2</sup> However, most of the bacteria found in the normal excreta are dead and harmless. They have been alive and active in the fluid contents of the cecum and ascending colon, but die as fluid is abstracted during the passage of the stool toward the rectum. The normal flora seem to be friendly toward the human host by discouraging the growth of pathogenic bacteria. The common bacteria of the colon produce very little exotoxin and scarcely any endotoxin. It is believed by most authorities that the pathogenic bacteria and protozoa are harmless so long as they are unable to attack the intestinal mucosa and produce larger or smaller ulcerations. Where ulceration occurs, diarrhea rather than constipation is usually found. We must acknowledge the fact that bacteria have been found in the lymph nodes of the mesentery in instances where gross ulcerations of the bowel have been lacking. However, it is very doubtful whether any symptoms appear unless the body resistance is lowered to the point where

the defense mechanisms are inadequate to destroy these bacteria as they invade the blood stream and other organs. The symptoms, then, are not those usually considered to be associated with intestinal toxemia but rather the symptoms are those we consider to be associated with such clinical entities as pyelitis, arthritis and lymphadenitis.

The evidence presented thus far has failed to show satisfactorily that the symptoms ascribed to constipation, biliousness or auto-intoxication are due to intestinal absorption. We believe that several other factors in this problem are of much greater significance:

1. Nervous disturbances.
2. Abnormalities of gastro-intestinal motility.
3. Allergy.

The profound effect of the emotions on gastro-intestinal functions has always interested our profession. The patient who has been symptom-free suddenly is brought face to face with a serious emotional crisis—the loss of a loved one or the devastating effect of disaster. He may experience all the gradations of anxiety and fear, even to despair and melancholia. During this cycle, the bodily functions undergo marked disturbances, and digestion and elimination are upset. In the acute phase of the anxiety, there is loss of appetite, a dry mouth, bad taste, rumbling in the bowels, often mild or severe abdominal cramps and diarrhea or constipation. Later, as the psychic trauma continues, the anorexia remains, the tongue becomes heavily coated, the patient is fatigued, body aches develop and head pains, dizziness, constipation and all the symptoms of biliousness color the picture. In such instances, it is difficult to explain all the mechanisms which are effective. We feel reasonably certain that for a time at least, there is inhibition of digestive ferments, probably inhibition of bile formation and most important, disturbances in gastro-intestinal motility. In such an hypothetical case, we have very little reason to suspect that intestinal toxemia is a matter of any moment. Likewise, it seems that in nervous shocks, similar disturbances of less severity are set up which, in sensitive peo-

ple, produce a chronic malfunction of the digestive tract and the symptoms of chronic intestinal toxemia result. This phase of the problem is discussed in interesting detail by Alvarez.<sup>3</sup> Very frequently, patients are unwilling to accept as a fact the functional origin of their trouble, because their point of view is colored by the blatant radio advertising of nostrums for the relief of "excess acid," "auto-intoxication," etc. The popular notion that any excretion that smells badly must be poisonous does not extend to some of our most delectable articles of food which may be anything but pleasant to the nostrils. The laity are sensitized to the horrors of intestinal putrefaction and constipation.

Disturbances in gastro-intestinal motility produce the majority of the symptoms of abnormal digestive function. Although this important subject cannot be discussed in any great detail, our experience has shown that many of the bilious symptoms occurring with constipation are the result of a spastic or irritable colon. Many years ago, Sippy drew attention to the disturbing effects of the "irritable" colon and more recently Kantor<sup>4</sup> and others have described the syndrome of the "unstable" colon. Among the intellectual class of patients, spastic constipation is an exceedingly common finding. Usually, the spasm occurs in the distal descending and sigmoid colon and very often but not invariably this is associated with gastro-intestinal hypermotility up to the point of spasm. Not infrequently the barium meal, which under normal conditions reaches the distal colon in twelve hours, will arrive there in four or five hours, but the defecation reflex does not take place. With this, there is abdominal distress accompanied by cramps, rumbling, occasional expulsion of gas and a heavy or sore sensation in the lower abdomen, especially on the left side. When the stools are passed, they are pencil-like, segmented or formed by a mass of small, elongated or spherical masses. In severe cases, mucus or blood is seen from time to time. Hemorrhoids may occur as a secondary complication. This condition is the result of an hypertonic, autonomic nervous system, which is often styled "vagotonia." The habitual use of cathartics ag-

gravates the irritability of the colon, or it may be the important initiating factor. The use of laxatives containing phenolphthalein, cascara or both are especially harmful, and whether phenolphthalein is taken as such, eaten in candy form or chewed in gum, it still tends to overstimulate the colon.

Everyone has experienced the feeling of well-being that surges over the body almost immediately after a normal bowel evacuation. A similar sense of relief after a copious catharsis comes to the nervous patient who is constipated and has bilious symptoms. By no stretch of the imagination can we convince ourselves that this relief is due to the sudden elimination of toxins; the reaction is entirely too prompt for that. A much more rational explanation appears to be that the overloaded distal colon is relieved of spasm at least temporarily, and that the unpleasant afferent impulses that have been crowding into the optic thalamus are suddenly stopped. There is a sudden feeling of relief and the feeling tone of the body rapidly returns to normal. Unfortunately however, in those people who have acquired the "cathartic habit," the spasm returns in a short time only to be relieved again but less effectively by catharsis. We are inclined to believe that the relief of spasm is of much greater importance than is the mechanical unloading of the bowel. In constipated, nervous patients with insomnia, sleep is often obtained promptly following the use of a small enema of plain water or normal saline solution (not soapsuds) before retiring at night. The relief is mechanical, not chemical.

Relatively little of scientific value can be said in regard to the rôle of allergy in the production of symptoms of chronic intestinal toxemia. The cutaneous and intracutaneous tests for food allergy are of some diagnostic importance, but not in a high percentage of cases. The use of a food diary, if kept properly, will give additional information; however, we must recognize the probability that most normal people are allergic to some food and hence we are at a loss to evaluate many of the positive reactions that occur in patients with gastro-intestinal symptoms. When careful questioning elicits a history of urticaria, hay fever, asthma, frequent colds or other disturb-



ances which are known to be caused by or aggravated by allergy, we may assume with greater authority that the digestive symptoms are allergic in origin. In many instances, the patient knows what foods disagree with him and volunteers the information that "milk poisons me" or "if I eat fish, I am in for a sick headache." Experimental and clinical experience in the future will help to clarify this important subject.

The treatment of the symptoms usually attributed to chronic intestinal toxemia includes many of the measures outlined in the treatment of splanchnoptosis. Attention is especially directed to the care of:

1. Nervous tension.
2. Habits of living.
3. Food and drink.
4. Bowel elimination.
5. Medication.

Treatment of nervous tension will require one or more consultations in which the problems of business, sex and the home are discussed in a confidential manner. No set rules of procedure can be followed, since it is obvious that each patient presents an individual problem. An immediate period of rest or a vacation is frequently imperative. The patient's attention to the details of his problem followed by a clear analysis often will enable him to suggest a satisfactory solution. In such cases, our accumulated experiences in dealing with nervous patients can be utilized to good advantage. Very often, the patient passes from a stage of bewilderment and anxiety to a state of increasing self-confidence. He must be given a clear and simple explanation of his trouble and above all, the clinical examination must be thorough enough to exclude, as far as possible, any organic basis for his complaints. This will do much to reassure the patient.

Instructions regarding habits of living must not be stereotyped but must be designed to conform with the occupation and social status of the patient. It is obvious that the key-stone is temperance in all things—work, play, sex habits, eating and drinking. Aristotle taught us centuries ago that the

temperate life is the happiest and the most satisfactory, and there is no reason why we should deviate from this fundamental principle, even though the patient be a busy executive. Other things being equal, the average man can smoke 6 to 10 cigarettes or 2 or 3 light cigars a day, but it is better to avoid smoking until after the noon meal. Much diversion and relaxation will result if a good hobby is developed. Treatment must be directed so that relaxation and a reasonable tranquillity of mind are habitual.

The diet of these patients should be well balanced. In the obese, sugars and starches should be reduced. In the undernourished, a high vitamin, high calorie regimen should be prescribed. In the majority of cases, a smooth, rather low residue diet is prescribed especially for those patients who have the spastic "unstable" colon. When normal bowel regularity is attained, the diet is modified by the gradual addition of more bulky foods containing vegetable fiber. The following smooth diet may be used as a guide:

#### SMOOTH—LOW RESIDUE DIET

##### *Breakfast:*

Orange or grapefruit juice, strained or puréed cooked fruits.

Eggs—one or two.

Bacon (well masticated).

White bread and butter, toast, zwieback.

Any smooth cooked cereal such as farina, cream of wheat, rice, cornmeal or strained rolled oats. Corn flakes, puffed rice.

##### *Lunch and Dinner:*

Broths, bouillon, cream soups with puréed vegetables.

Meats, scraped or finely ground.

Beef.

Lamb.

Fresh pork, lean and well cooked.

Chicken and turkey.

Squab.

Fresh fish, not fried.

Oysters.

If meat is tender and is well chewed, grinding may be omitted.

##### *Vegetables:*

Puréed vegetables as peas, carrots, asparagus, cauliflower, squash, tomatoes. (Omit spinach, string beans, and beets.) White potato mashed, boiled or baked (no skin).

## Bread:

White bread, toast, biscuits cut thin and toasted.

## Salads:

Tomato aspic, canned fruit salads (omit pineapple).

## Desserts:

Puddings: rice, tapioca, custard, blanc mange.

Jello (plain), junket, ice cream, ices, fruit whips.

Stewed peaches, pears, apricots (well chewed).

Simple cake.

Baked bananas.

## Beverages:

Weak tea and coffee.

Kaffee Hag and Sanka coffee.

Boiled milk.

Cocoa.

Postum.

Butter, cream and mayonnaise as desired.

Avoid all highly seasoned foods.

It is important to avoid all foods containing tough skins, seeds, rough fiber and bran.

Do not swallow any food that is not smooth or very well chewed.

When there is reason to suspect food allergy, the foods which seem to give offense are omitted; most frequently these are milk, wheat and eggs. The use of liquids with the meal are permitted in moderation but tea and coffee are prohibited for a time. Alcoholic beverages, with the exception of light wines, are contraindicated. Beer may be tolerated well by patients who have no idiosyncrasy and who find that it is a pleasant stomachic.

The bowel management is well outlined by Kantor.<sup>4</sup> He states that the frequency of the cathartic habit in the absence of constipation is rather high, and he emphasizes the importance of therapeutic measures directed toward the restoration of normal bowel function. He cites the three R's of successful bowel treatment—reassurance, relaxation and reeducation and he recommends the following procedures:

(a) Withdrawal of all cathartics.

(b) Mild sedatives to promote relaxation and sleep.

(c) Belladonna.

- (d) Bland diet.
- (e) Adequate intake of fluid.
- (f) Lubrication with mineral oil.
- (g) Use of agar-agar.
- (h) The occasional use of koalin or x-ray barium to allay irritation.

In our practice, we usually advise that the mineral oil be used night and morning in 1-ounce doses. Agar-agar is given in the flake form—2 teaspoonfuls after each meal, if it is well tolerated. The dosage is reduced as the condition of the bowel improves.

For medication, we prescribe 10 drops of tincture of belladonna after meals increasing the amount to 12 or 14 drops, until the mouth becomes dry, and then the dose is diminished to three fourths of this amount. To secure relaxation, 10 grains of sodium bromide with 10 minims of tincture of hyoscyamus is used three times a day. It is rarely necessary to use any other drugs unless the bromide produces furunculosis; in such a case,  $\frac{1}{4}$  grain phenobarbital is used. Four drachms of tincture of nux vomica and 4 drachms of dilute hydrochloric acid U.S.P. in a 4-ounce mixture taken in a teaspoonful of water before meals will help to stimulate better gastric secretion. In general, however, belladonna or atropine and a sedative are adequate.

Some evidence exists which suggests that mineral oil may carry out some of the important and essential vitamins before absorption takes place. If this proves to be correct, then the use of lubricating oils should be discontinued as soon as the colon returns to normal function.

Much more could be said about the problem of intestinal auto-intoxication and biliousness and the literature contains many articles on various aspects of the disease. When the treatment is directed to a correction of the known physiological disturbances, and when it is based on a careful study of each patient, the results will justify fully the expenditure of time and effort.

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## DIAGNOSIS OF CANCER OF THE COLON

THOMAS E. JONES

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THE insidious manner in which malignancy of the colon begins demands the most painstaking care in eliciting the history and making the examination. Uniformity of signs and symptoms do not occur because they vary according to the location of the lesion in the colon.

In the proper interpretation of the symptoms of which the patient complains, it will be well to remember that because of its embryological development, anatomical variations, and physiological function, the colon differs in its various parts. The right side of the colon (the cecum, the ascending colon and half of the transverse colon) is formed from the midgut. Anatomically, the lumen is much larger, the walls are thinner and the blood and lymphatic supply are very plentiful. From a physiological standpoint, the contents of the right half of the colon are liquid, and absorption of water takes place. The left half of the colon (from the mid-transverse colon to the rectum) is developed from the hind gut. Its lumen is smaller, its coats thicker, and its blood and lymphatic supply is less than that of the right half. The contents of this part of the bowel are solid and its physiologic function is that of storage. Consideration of all these factors will then make it clear that it is impossible to have only one group of symptoms for cancer of the colon.

Cancer of the right side of the colon generally manifests itself in a disturbance of physiologic function. Due to altered physiology, some of the earliest symptoms are weakness, loss of weight and anemia. This occurs long before any mass is palpable. There are no obstructive symptoms because the

contents are liquid, the lumen is large and the growth flat. The patient frequently complains of indigestion and of vague epigastric distress which simulates chronic appendicitis. Constipation is not common, but there may be occasional attacks of diarrhea. In any case of unexplained anemia, the stool should be examined for occult blood and the presence of a carcinoma of the cecum should be considered.

In lesions of the left side of the colon, however, constipation and obstructive symptoms of pain and cramping frequently occur for the reasons mentioned before—since the stool is firm in consistency, the bowel lumen smaller, and the growths tend to encircle the bowel. Because of the proximity to the anus, straining and the trauma of the hard stool, gross blood is frequently seen. A lesion in the sigmoid or rectum, in which location most malignancies of the bowel occur, causes considerable mucous discharge, and there is urgency of bowel movements and so-called “diarrhea.” I believe that this latter symptom leads to a number of errors in diagnosis. The physician too frequently associates cancer with constipation and obstruction, and when the patient complains of frequent bowel movements, the possibility of the presence of malignancy is not investigated thoroughly, and too often the patient is dismissed with a prescription for paregoric. These frequent bowel movements are not due to true diarrhea, but represent emissions of mucous, pus and blood. An examination of the stool makes many a diagnosis for the pediatrician; it will do the same for those who care for adult patients. Even though the patient complains of diarrhea, examination of the stool may convince the physician that further investigation is essential.

Another type of malignant growth of the left side of the colon, which may give a different and rather characteristic picture and one which deserves mention here, is the annular lesion which produces the napkin-ring type of deformity. In its early stage, it involves the muscularis and will produce constriction. Often an acute obstruction is the first symptom noticed by the patient. Occasionally, it is not complete during

the first attack and it may be weeks or months before the patient experiences another attack. This group constitutes, however, a very small percentage of the total cases.

In making the diagnosis of cancer of the colon then, the physician should make the following examinations in the order named: a careful history and physical examination, digital, proctoscopic and sigmoidoscopic examination, and lastly, roentgen examination. When one realizes that from 75 to 80 per cent of these growths are readily diagnosed by digital or sigmoidoscopic examinations, it is quite obvious that roentgen examination should be resorted to only after other simple procedures fail. Furthermore, a moderately early cancer of the rectum may frequently be overlooked on roentgen examination and in advanced cases, filling the colon with barium may precipitate an obstruction which requires an emergency colostomy. Roentgenography is an invaluable aid and I have the greatest respect for it and its usefulness, but it must never be used first to the exclusion of all other methods of diagnosis.

In eliciting the history then, we must inquire carefully regarding the function of the gastro-intestinal tract. Generally one learns that there has been a change in the patient's bowel habits; from a perfectly normal routine, he has noticed some irregularity, or constipation has alternated with diarrhea. Frequently, there will be a feeling of uneasiness or rumbling in the bowel or a sensation of incomplete evacuation. A change in color of the stool or the presence of blood in the stool may have been noticed. Lesions in the cecum generally give rise to discomfort above the umbilicus, while those in the sigmoid give rise to pain below the umbilicus. However slight, these symptoms must be investigated thoroughly. Loss of weight is not a very early symptom.

On physical examination, the color of the mucous membranes must be noted as well as the texture of the skin. The lymphatic glands in the supraclavicular space are palpated for occasionally metastasis may have occurred from a carcinoma of the sigmoid and rectum, although this does not happen as frequently as from a carcinoma of the stomach. Palpation of



the abdomen for masses must be carried out in a routine manner from the sigmoid to the cecum and the liver must be felt for carefully. If the growth is in the lower 2 inches of the rectum or anus, palpable inguinal glands may be found. From a laboratory standpoint, blood studies are particularly indicated.

For the digital examination of the rectum, it will add a great deal to the comfort of the patient if the entire length of the finger is lubricated with K.Y. jelly rather than merely placing a small bit of vaseline on the tip of the finger, as is usually done. The examination is best carried out with the patient bending over a table. By having the patient bear down it will frequently bring in contact with the palpating finger a growth which would not be discovered otherwise. Next in order is a sigmoidoscopic examination preliminary to which it is necessary to have a clean bowel. This may be accomplished by saline laxatives or by enemas. The sigmoidoscopic examination is best accomplished with the patient in the knee-chest position or on a tilt table. After the sigmoidoscope is introduced into the rectum, the plunger should be removed so that insertion from then on is done under direct vision and not pushed up blindly. With the use of air inflation, the scope may be introduced from 10 to 12 inches in most cases; however, this occasionally is impossible due to congenital kinks, bands or inflammatory processes. Force must never be used in manipulating the scope. If a lesion has been demonstrated by this means, biopsy may or may not be taken, according to the experience of the examiner. In case a lesion has not yet been demonstrated, roentgen examination must be made and the patient should be referred to the roentgenologist with some indication as to what the physician expects to find. Too often, the physician orders a certain type of examination which will prove to be incomplete. The roentgenologist should be used as a consultant and should have the liberty of carrying out whatever type of examination he feels is indicated in order to determine the presence or absence of a malignant lesion of the colon.

If all these examinations reveal no abnormalities, the patient should not be dismissed if there is the slightest suspicion that a malignant lesion may be present, because a negative x-ray examination may lead to a false sense of security. The physician should examine the patient at monthly intervals to be sure that the symptoms do not persist, and if they do even with negative findings, exploratory operation should be resorted to in any suspicious case.

In the differential diagnosis of lesions in the right colon, tuberculosis, actinomycosis, and amebic ulceration must be considered. Actinomycosis is quite rare, and tuberculosis is generally associated with pulmonary involvement which may be revealed by x-ray of the lungs. The prevalence of amebic dysentery, which in the last few years has proved to be endemic, frequently may present difficulty, and in cases in which it is suspected, the stool should be examined for amebae. In the left side, amebic ulceration, diverticulitis and endometriosis involving the sigmoid in women must be differentiated. Obstruction without bleeding, the presence of pain and fever and x-ray examination will frequently rule out diverticulitis, while the diagnosis of endometriosis in women is generally made from the history, the disturbance being of long standing, and lower abdominal pain or rectal symptoms being generally augmented during the menstrual period.



## DIET IN THE TREATMENT OF ARTHRITIS

RUSSELL L. HADEN

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ARTHRITIS is not a single disease but a group of diseases with little in common except joint involvement. Any discussion of diet in the treatment of joint disease must take into consideration the widely different etiologic factors and clinical classes. Clinically, arthritis may be grouped satisfactorily as follows:

1. **Rheumatic fever** in which the cause is unknown. This has been thought to be due to the direct toxic action of bacteria or to the reaction of an allergic joint to bacteria, probably streptococci. Just now there is much data indicating that a filtrable virus may be the causative organism, the activity of which in turn may be initiated by the streptococcus and other bacteria.

2. **Specific infective arthritis** due to joint invasion by specific types of bacteria such as the gonococcus, the staphylococcus, the *Streptococcus hemolyticus*, or the pneumococcus. Here the joint disease represents a metastatic localization in the joint from a bacteriemia arising in an infected focus. This is usually an acute process which may become chronic.

3. **Arthritis due to traumatism** such as the "golfer's shoulder" and "tennis elbow." The joint symptoms are the direct reaction of joint tissue to mechanical injury.

4. **Arthritis Occurring as an Incident in the Allergic State or in Some Constitutional Disease Such as Hemophilia, or in Neurogenic Disease Such as Tabes Dorsalis or Syringomyelia.**—In the allergic state, there is a transudation of fluid into the joint covering or periarticular tissues; in hemophilia, the joint disease is due to hemorrhage

into the joint with consequent cartilage destruction and secondary changes. In *tabes dorsalis* or other neurogenic diseases, there is primary degeneration of joint cartilage probably due to excessive trauma in an anesthetic joint.

5. **Gout.**—This is a metabolic disturbance with protean manifestations. It is primarily a chemical disturbance during the course of which urates are deposited in joint cartilage and the surfaces are much irritated, producing the picture of arthritis. The accumulation may be due to impaired excretion of uric acid or to a difficulty in oxidation in the body tissues.

6. **Chronic rheumatoid arthritis** in which the disease is localized primarily in the synovial membrane and periarticular tissues. The cartilage here may also be involved but always secondarily. This disease is probably closely related to rheumatic fever and the etiology is still unsolved. Even if there is one etiologic agent, the activity of the causative agent is certainly influenced by many factors.

7. **Chronic hypertrophic arthritis** which is due to a primary softening or degeneration of joint cartilage secondary to a disturbance in nutrition of the cartilage. This disturbance is a manifestation of the wear and tear of tissues which may be initiated or influenced by impaired nutrition from any cause, circulatory changes, increased weight bearing, decreased metabolic rate with consequent defective combustion, and various chemical disturbances impairing the integrity of joint cartilage.

It is apparent from this clinical grouping that many cases of arthritis have no relation to diet except insofar as any disease process is influenced by any factor impairing the general health. Thus in specific infective arthritis, rheumatic fever, traumatic arthritis, constitutional or neurogenic arthritis, usually the only indication is for a completely well-balanced diet unless a special diet is indicated for the disease in which the arthritis is an incident. If allergy is a factor, food allergy must be studied and the diet adjusted in accordance with the results of the allergy tests. An anemia often develops rapidly

in rheumatic fever or in arthritis due to specific bacteria, so this should be taken into consideration and foods for the correction of the anemia should be supplied abundantly. These are liver and red muscle meat, fruits which stimulate blood formation—especially peaches and apricots, vitamin C in the form of oranges and grapefruit or iron in the form of prunes and raisins—and the iron-containing vegetables such as spinach and lettuce.

When gout is the only factor, it should be treated specifically by diet in an attempt to decrease the uric acid in the blood and tissues by limitation of the intake of purine-containing substances from which uric acid is formed. Patients suffering from gout are often overweight, so weight reduction is frequently necessary also.

#### DIET FOR GOUT

*Breakfast:* fresh fruit, cereals with cream, eggs, bacon, toast, wheat or buckwheat cakes with maple syrup, caffeine-free coffee.

*Lunch:* vegetable or cream soup prepared without meat stock, eggs, cheese, tomato and bacon sandwich, vegetable salad, ice cream or pudding, milk.

*Dinner:* vegetable or cream soup prepared without meat stock. Meat substitutes made with cheese such as cheese soufflé and Welsh rarebit, macaroni, rice, potatoes, corn, tomatoes, cabbage, cauliflower, turnips, squash, lettuce, celery, onions, string beans, carrots, broccoli, asparagus, brussels sprouts, bread, fresh or preserved fruits, vegetable salads with French or mayonnaise dressing, cottage cheese, puddings made with rice or tapioca, nuts, ice cream, milk, weak tea, or caffeine-free coffee. The following foods should be avoided: sweetbreads, liver, kidney, herring, sardines, anchovies, bouillon, sea foods, poultry and other meats, spinach, peas and beans.

If the patient is overweight, a 1000-calorie diet should be satisfactory. Such a diet selected from the above list would be:

*Breakfast:*

Fruit .....	1 serving
Egg .....	1
Toast .....	1 slice
Butter .....	1 square
Caffeine-free coffee .....	As desired

*Luncheon:*

## Cream soup, with:

Milk—whole .....	$\frac{1}{2}$ glass
and	
Vegetable .....	$\frac{1}{2}$ cup
Vegetable—cooked .....	$\frac{1}{2}$ cup
Vegetable—raw .....	1 cup
Butter ..	1 square
Milk—skimmed .....	1 glass
Fruit ..	1 serving

*Dinner:*

Cheese .....	2 ounces
or	
Eggs .....	2
Vegetable—cooked .....	$\frac{1}{2}$ cup
Vegetable—raw .....	1 cup
Butter ..	1 square
Milk—skimmed .....	1 glass
Fruit ..	1 serving

Chronic rheumatoid (atrophic) arthritis has little in common with degenerative arthritis described below except joint involvement. Here the patient shows evidence of a generalized disease as indicated by loss of weight, multiple joint involvement, anemia, malaise, and disturbed circulation. The joint picture is that of an inflammatory disease. So far, no one causative agent has been discovered. All the evidence indicates that an infection is concerned in its etiology but that the cause is influenced by numerous factors. Careful studies of well-developed cases show frequently a marked anemia of the iron deficiency type, an achlorhydria, some variation from normal in the metabolic rate, a diabetic type of glucose tolerance curve, sometimes an excess of uric acid, a redundant colon possibly due to a defect in supply or utilization of vitamin B<sub>1</sub> and often underweight.

Certainly no one diet is suitable for all cases of chronic rheumatoid arthritis. Since the etiology is still obscure, many different diets have been proposed for its treatment, usually without any scientific basis. Here, as in any chronic disease, a well-balanced diet should be supplied. So many patients have been on a diet deficient in the protective foods and frequently in meat, that the need for the foods containing vitamins, mineral salts and protein should be especially emphasized.

I believe it unwise, however, to simply effect a gain in weight in a patient suffering from rheumatoid arthritis by means of a high-calorie diet with the idea that the patient's resistance is thereby increased. Such a patient often cannot use the food elements offered so there is no point in offering more. This is probably the explanation for the hypochromic anemia seen so frequently. Likewise, the diabetic type of glucose tolerance curve indicates that the body cannot utilize the sugar offered it. The body in such a state may be thought of as having a chemical overload. Rest, which, after all, is the most valuable therapeutic agent in the disease, should include chemical rest as well as physical and mental rest.

Unless a patient with chronic rheumatoid arthritis is underweight due to a deficient food intake, his condition is usually improved little by simply increasing the total food intake. In my experience, most patients do best at the beginning of treatment at least, on a low-carbohydrate, high-vitamin diet, since this gives ample calories and supplies the food elements probably most indicated. After improvement is under way, the carbohydrate intake is gradually increased, although one often finds a sufficient weight increase on the original diet. Since the problem is often to get the patient to metabolize what is given, we usually give insulin for a time if the glucose tolerance curve shows a defect in sugar utilization or if the patient is without appetite.

We have used the following diet for chronic rheumatoid arthritis:



## HIGH-VITAMIN, LOW-CARBOHYDRATE DIET

This diet includes abundant meat, fruits and vegetables with a minimum of sweet and starchy foods.

1. Eat a liberal portion each day of any fresh fish or meat such as beef, lamb, chicken.

2. Eat one or two eggs each day.

3. Take fresh vegetables both raw and cooked as follows:

(a) Eat two fresh raw vegetables from the following list.

These may be taken in salad form.

Cabbage	Endive	Radish
Carrot	Lettuce	Swiss chard
Celery	Onion	Tomato
Cucumber	Pepper	Water cress

(b) Eat at least two fresh-cooked vegetables from the following list.

Asparagus	Celery	Peas
Beets	Egg plant	Rhubarb
Broccoli	Kale	String beans
Brussels sprouts	Kohl rabi	Spinach
Cabbage	Mushrooms	Squash
Cauliflower	Onion	Tomato
Carrots	Parsnips	Turnips

4. Take fruit, especially fresh fruit in season, liberally each day. It is a good plan to eat fruits in place of made desserts and pastries; oranges, grapefruit, pears, pineapple, melon, berries and apples are especially good. Use just sufficient sugar to make the fruit palatable.

5. Drink two glasses of milk or buttermilk each day. Other beverages with a minimum of sweetening may be added.

6. Eat no cereal or bread except two slices of whole wheat bread daily.

7. Take butter, cream and salad dressings as desired.

8. Eat nuts as desired.

9. Add vitamins to those in foods as follows:

(a) Wheat germ for vitamin B. Take two tablespoonfuls each day.

(b) Fresh yeast for vitamin B. Take two cakes each day.

(c) Cod liver oil or substitute for vitamins A and D, such as two tablespoonfuls of cod liver oil twice a day, or 1 ABD capsule or halibut liver oil with viosterol three times a day.

10. Avoid the following:

All vegetables not on list.

All bread and bread substitutes, except the whole wheat bread allowed.

All cereals.

All desserts such as puddings, cookies, pies, cake, pastry and ice cream.

All very sweet fresh fruits and all dried fruits such as figs, dates, raisins and prunes unless taken only occasionally in small amounts.

All spaghetti, noodles, macaroni, rice, candy, honey, syrups, jellies.

All sugars except such as are necessary to make the food and drink palatable.

An adequate (1800-calorie) diet selected from this list with household measures is indicated below:

*Breakfast:*

Fruit	1 serving
Wheat germ	2 tablespoonfuls
Eggs	2
Toast—Whole wheat	1 slice
Butter	1 square
Cream	$\frac{1}{2}$ cup
Sugar	1 teaspoonful
Coffee or Tea	As desired

*Luncheon:*

Meat or meat substitute	2 ounces
Vegetable—cooked	$\frac{1}{2}$ cup
Vegetable—raw	1 cup
Mayonnaise or oil dressing	1 tablespoonful
Bread—Whole wheat	$\frac{1}{2}$ slice
Butter	1 square
Milk	1 glass
Fruit	1 serving
Sugar	1 teaspoonful

*Dinner:*

Meat or fresh fish .....	4 ounces
Vegetable—cooked .....	$\frac{1}{2}$ cup
Vegetable—raw .....	1 cup
Mayonnaise or oil dressing .....	1 tablespoonful
Bread—Whole wheat .....	$\frac{1}{2}$ slice
Butter .....	1 square
Milk .....	1 glass
Fruit .....	1 serving
Sugar .....	1 teaspoonful

*Cream and Butter.*—At least  $\frac{1}{2}$  cup of cream and 3 squares of butter should be used daily. More salad dressing may be used if desired.

*Sugar.*—Do not use more than 3 teaspoonfuls daily.

After the patient has begun to improve, additions are allowed in the form of more whole wheat bread, baked potato or cereal and certain desserts such as ice cream. These are additions, however, to the basic diet outlined and not to replace any of the essential foods.

Chronic hypertrophic arthritis or primary degenerative arthritis occurs to a certain extent in every person past middle age and is an expression of wear and tear on joint tissue, but usually the pathologic changes are not extensive enough to cause symptoms. The disease may be accelerated by any condition which will age tissues, especially physical and nervous exhaustion, low metabolic rate, vascular disturbances or toxic absorption from the alimentary tract or from areas of infection. The initial quality of the joint as determined by heredity is most important. This disease is frequently associated with obesity, arterial hypertension or hypotension, arteriosclerosis and diabetes. The proved metabolic disorders of the joint, such as gout and alkaptonuric arthritis, produce anatomic changes in the joint which are similar roentgenographically to those in primary degenerative arthritis. There is much evidence to suggest that this type of arthritis is a chemical disturbance in the nutrition of the joint cartilage. It comes at a time of life when from a chemical standpoint the capacity of the body tissues to function normally is impaired. The patient is frequently overweight and this usually is secondary

to a lowered metabolism. The added weight is also an additional mechanical insult to the joint cartilage. The blood uric acid is frequently elevated and the glucose tolerance curve often indicates diminished carbohydrate utilization. Many of the patients have had a poorly balanced diet with excessive starch intake for a long time. It seems probable that the dietary imbalance is often responsible for a diminished utilization of vitamin B. While the cause of arteriosclerosis is unknown, it seems that the cholesterol metabolism is related to it, and this in turn is related to the lowered metabolic rate and the diet. Arteriosclerosis is responsible for the obliteration of the fine capillaries which are certainly partly responsible for the impaired nutrition and consequent softening of the articular cartilage. The diet in this type of arthritis is of prime importance, the indication usually being to supply a diet which puts as small a metabolic load on the patient as possible, is properly balanced and sufficiently low in calories. We have used a low-calorie diet selected from the low-carbohydrate, high-vitamin diet given above. Nuts are eliminated. Butter, cream and dressings are allowed for seasoning only. Eggs are omitted. All food is taken in small amounts. The following is a low-calorie (1000) diet selected from this list:

*Breakfast:*

Fruit	1 serving
Wheat germ	2 tablespoonfuls
Toast—Whole wheat	1 slice
Butter	$\frac{1}{2}$ square
Coffee or Tea	As desired

*Luncheon:*

Lean meat or substitute	2 ounces
Vegetable—cooked	$\frac{1}{2}$ cup
Vegetable—raw	1 cup
Bread—Whole wheat	$\frac{1}{2}$ slice
Butter	1 square
Milk—skimmed	1 glass
Fruit	1 serving

*Dinner:*

Lean meat or fresh fish . . . . .	2 ounces
Vegetable—cooked . . . . .	$\frac{1}{2}$ cup
Vegetable—raw . . . . .	1 cup
Bread—Whole wheat . . . . .	$\frac{1}{2}$ slice
Butter . . . . .	1 square
Milk—skimmed . . . . .	1 glass
Fruit . . . . .	1 serving

If a patient with chronic degenerative arthritis is overweight or even if he is underweight and is having active symptoms from the disease, it is often most valuable at the beginning of treatment to keep him in bed for five days and to give orange juice or other fruit alone. The first day the patient is given only the juice of one orange and water is denied; no other food is permitted. The juice of an additional orange is given each day so that by the fifth day five oranges are given. At the end of this time, a 500-, 800-, and 1000-calorie diet from the list given is allowed as indicated. The length of time the intensive restriction of carbohydrate-rich food, if kept up, will be determined by the weight and general symptoms of the patient. It is best to continue indefinitely with a diet just sufficient to maintain the weight at the desired level, thus insuring the proper metabolic balance. If the diet is increased, an additional chemical strain is placed on the body to metabolize this food in order that it may either be stored as fat or excreted as end-products.

## SUMMARY

No one diet is suitable for the treatment of patients with arthritis, although dietary measures are of great aid in the management of joint disease.

In those cases of arthritis in which the joint involvement is part of some general disease, there are no dietary indications other than those best for the systemic disease.

Gout is the only joint disease treated specifically by diet, but even here the dietary management is only part of the treatment of the disease.

In most cases of chronic rheumatoid arthritis there is a

marked physiologic disturbance. Frequently there are manifestations of nutritional deficiency disease as well as other metabolic variations from the normal. The diet should be high in protective foods which supply vitamins and mineral salts, adequate in protein and low in carbohydrate at the beginning of treatment. Later, the calories may be increased by adding to the carbohydrate content.

Chronic degenerative arthritis is a phase of the general slowing up of body chemical processes which naturally are the result of age and use and which unnaturally are the result of various extraneous factors. The dietary indication is to give the body as small a chemical or metabolic load as is required and to supply foods which give the most valuable nutritional elements.



## THE TREATMENT OF EMACIATION

R. H. McDONALD

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EMACIATION is a very general term which denotes insufficient nutrition of the body tissues. It may be due to three main causes: (1) insufficient caloric intake, (2) disturbances of digestion or assimilation from the gastro-intestinal tract, or (3) to increased katabolic processes within the body. Insufficient caloric intake is seen in starvation due to a lack of available food or improper diet. Such emaciation has an economic bearing because the condition is caused entirely by a lack of all or part of the required carbohydrates, fats, proteins, minerals and vitamins necessary for normal nutrition. Disturbances of digestion or assimilation are largely due to mechanical factors in the gastro-intestinal tract which prevent proper function—such factors are gastric carcinoma or gastrocolic fistula. The third main group includes all the varied disturbances which result in increased metabolism and among these conditions are tuberculosis, diabetes, the blood dyscrasias and neoplasms of all types.

It is obvious that emaciation is a symptom only and no attempt to treat the patient with this symptom should be made until a very careful diagnosis has established the etiology of the condition. Specific therapy can then be prescribed for the removal of the etiological factor if such be possible. It is equally obvious that no universal method of treating malnutrition can be advanced; rather each patient must be treated individually, although certain general principles are applicable in all cases.

The normal diet must contain sufficient energy-yielding food to supply the basal energy requirements in addition to



that required to meet the energy expenditures of activity. Energy may be derived from the oxidation of proteins, carbohydrates or fats, although under ordinary conditions, the greater amount of energy is derived from carbohydrates. Adequate protein must be included to supply the essential amino-acids and sufficient amounts of carbohydrates and fats must be included. The diet must also contain mineral salts of sufficient quantity and quality to maintain the skeletal structure, to preserve equilibrium between the fluid portions of the body and to supply specialized metabolic needs. The diet must also include those substances which largely are of unknown chemical nature but which are necessary for normal health—these are the accessory food factors or vitamins—and an adequate amount of water is essential to allow solution of electrolytes and to preserve proper tonicity of the body fluids. Finally, the diet must include sufficient bulk to supply the physical stimulus for peristalsis. As a general rule, approximately 40 calories per square meter of body surface must be taken to supply the basal requirement and to this must be added sufficient calories necessary for the extra energy required to meet activity. The satisfaction of this extra energy requirement varies greatly—the average adult male who sleeps eight hours and does office work will require approximately 2400 calories, whereas the active lumberman of equal size will require easily twice that amount to maintain his weight, and the six-day bicycle rider will require perhaps four times that amount.

Increased weight in the emaciated individual is dependent upon the ingestion and assimilation of food units in excess of that necessary for maintenance of the weight under usual activity. Excessive amounts of any of the food elements—proteins, fats or carbohydrates—are capable of increasing the weight. Usually the optimum protein intake lies between 100 and 120 Gm., larger amounts frequently disturbing the digestion. In convalescence where it is desirable to replace the lost body proteins, more concentrated protein foods—eggs, fowl, fish, beef, veal, milk and cheese—should be used. Increased

caloric intake is usually readily accomplished by increasing the amount of carbohydrates. For a healthy individual, the usual diet contains approximately 180 Gm. of carbohydrates which can be increased to 300 Gm., thus giving an additional 500 calories. Furthermore, the use of large amounts of carbohydrate has been shown to reduce the protein combustion and thus conserve the proteins of the body. Fat is the most readily available source of energy and represents the highest caloric value in the smallest bulk. The usual diet contains approximately 100 Gm. of fats and this can be increased to perhaps 250 Gm. with a consequent increased caloric intake of 1400 calories. Butter, cream and olive oil are fat-containing foods which should form part of the diet designed to increase weight.

The therapy of emaciation resulting from the increased metabolic processes accompanying the febrile illnesses is usually simple. In the febrile illnesses of short duration, such as pneumonia, the loss of weight is usually slight and no special attempt should be made during the course of the illness to increase the caloric intake, since the toxic gastro-intestinal tract does not tolerate or assimilate food well. During convalescence, increased caloric intake in the form of milk and cream mixtures, egg-nogs and flavored milk dishes is usually sufficient to restore the weight to normal. In the febrile illnesses of longer duration such as typhoid fever, where severe malnutrition may occur, the body tissues should be nourished throughout the course of the illness by the use of a diet high in calories. It has been demonstrated that the danger of perforation is not increased by such measures and the patient emerges in convalescence in a better condition. It is frequently advisable to feed patients every two or three hours during both the day and night and to arrange, if possible, for a total intake of 4000 calories in every twenty-four-hour period to combat the increased metabolism of the body resulting from the high, prolonged fever. Meat may tend to increase intestinal putrefaction, but sufficient protein in the form of eggs and milk must be taken to counterbalance this lack. A theoretical consideration has been advanced that fats

are less well oxidized in the patient with typhoid fever and that the intermediary products formed may increase the tendency to acidosis. Practically always, cream and butter are well tolerated. Carbohydrates may be given in large amounts preferably without cellulose content.

In the presence of any prolonged fever as pulmonary tuberculosis, it is generally agreed that the protein content of the diet should be slightly in excess of the ordinary bodily requirements. It has been shown that the traditional use of large amounts of milk and eggs has no special beneficial action and these foods should be used strictly in proportion to their food values. Fats are especially useful in these diseases, since it has been shown that it is desirable to keep the weight somewhat above the average considered to be normal.

In local diseases of the stomach such as carcinoma or gastric ulcer, where physiological rest for the organ is desirable, the use of transgastric or duodenal feeding will frequently enable the patient to retain weight and remain a great deal more comfortable. The duodenal tube may be left in place for twelve or fifteen days at a time and through it, the patient *should receive feedings every two hours, care being taken that the food is administered slowly.* All food should be strained and given at body temperature and this should be followed by a little water to prevent blocking of the tube. Milk, eggs, gruels, cereals, cream and normal saline solution may be given in this way and thus a high caloric intake may be insured.

In conditions which preclude feeding by mouth, certain artificial methods of feeding have been used, the oldest of which undoubtedly is rectal feeding. Unquestionably, the use of this method has been of some benefit, but in the majority of cases it has not proved to be a practical method of increasing the caloric intake. It is well known that water and salts may be absorbed from the colon and perhaps a certain amount of carbohydrates. Absorption of protein is very questionable and apparently fats are not absorbed at all. Attempts have been made to provide predigested protein products and monosaccharids, but the discomfort and inefficacy of the method

has led most clinicians to discard it. Subcutaneous feeding of proteins and fats has not proved to be practical, but solutions of glucose not stronger than 6 per cent have been absorbed very satisfactorily. The intravenous use of glucose in concentrations of 5 to 50 per cent in normal saline solution or distilled water has become an essential procedure in hospital practice for supplying extra calories, especially as a temporary method during severe disturbances of the gastro-intestinal tract. It should be administered slowly in order to avoid blood sugar levels which will allow a considerable portion of the glucose to spill over into the urine.

Metabolism may be affected greatly by thyroid hypersecretion and extreme emaciation is characteristic of the severe grades of hyperthyroidism when, despite a ravenous appetite, the markedly increased metabolism induced by the excessive thyroxin produces malnutrition. Increase in the caloric intake is impracticable. In such instances, surgical intervention in the form of subtotal thyroidectomy, although admittedly a gross form of therapy, has proven in clinical practice to reduce the excessive secretion with restoration of the normal balance. Postoperatively, the thyroid patient requires only a normal diet with some added caloric value to regain his normal weight. Failure to gain weight suggests insufficient removal of the gland or the presence of accessory thyroid tissue. In this connection, an interesting group of patients are those with malignant thyroids associated with hyperthyroidism in whom local resection gives temporary improvement with the development later of recurrent signs due to the production of thyroxin in distant metastases. Characteristically, insufficient thyroxin production, whether due to resection of too much of the gland or to idiopathic causes, is accompanied by excess weight, but in this regard, it must be remembered that some individuals who are underweight have a low metabolic rate. Such individuals tolerate thyroid extract well and may gain weight following the judicious administration of the extract. This apparently is due to the increased appetite produced by this medication.

The emaciation seen in Addison's disease is a result of gastro-intestinal disturbance and may be relieved by the use of the adrenal-cortical extract, although this constitutes replacement therapy and obviously does not cure the condition. Very severe grades of emaciation are seen in certain disturbances of the pituitary gland, the so-called "Simmond's disease," and therapy at present is unsatisfactory, but the use of newer pituitary hormones offers possibilities. The malnutrition characteristic of the poorly treated diabetic depends largely upon the constant loss of sugar through the urine coupled with the result of disturbed gastro-intestinal function. The proper use of insulin in addition to an adequate diet now permits a normal degree of nutrition for the diabetic, and such replacement therapy can apparently be continued for years, so that the diabetic now may experience his normal life expectancy. Under such management, the severe degrees of emaciation which commonly followed the starvation treatment used formerly have disappeared. It is well to remember, however, that the patient with diabetes should not be allowed to become overweight, and a degree of nutrition slightly under the normal for height and age tends to reduce the metabolic load and lessen the pancreatic strain.

The use of insulin in the treatment of malnutrition in non-diabetic patients received attention within a year of the discovery of the islet hormone, and investigators have arrived at widely divergent conclusions in regard to the value of this procedure. The usual method has been to give insulin in dosages of from 3 to 5 units, thirty minutes before meals, and gradually to increase the dosage until mild symptoms of hypoglycemia result. In most cases, an increased caloric intake has also been prescribed. The mechanism of the production of increased weight following insulin therapy is theoretical. Increased caloric intake or better assimilation of food undoubtedly are factors, the former in some cases being influenced by the fear of hypoglycemic reactions. Psychic stimulation of the appetite cannot be measured but must certainly be a factor in the sensitive individual. There appears

to be no consistent relationship between the blood sugar level and the appetite, although marked decreases in the blood sugar level undoubtedly cause a subjective sensation of hunger. It has been shown that the injection of from 10 to 20 units of insulin causes hunger contractions and an increase in gastric tonus in normal fasting subjects, and it may be that this insulin effect on the gastric muscle has much to do with the increased food ingestion which has been reported. It has also been reported that the injection of insulin increases gastric, biliary and pancreatic secretion, which would suggest improved digestion and assimilation of food as a basis for increased weight in undernourished patients. However, a true increase in weight can be attained only by increased caloric intake. In patients in whom increased appetite results from the use of insulin, benefit has been obtained. Such results are not universal and the method offers no specific remedy in the treatment of undernutrition.

#### SUMMARY

Severe degrees of undernutrition should be prevented by early recognition and relief of the etiologic factors. The treatment depends upon the ingestion and assimilation of an adequate diet of sufficient caloric value to provide energy not only for the basal metabolic needs and to cover whatever activity is carried on, but also to allow for some excess to produce a gain in weight. Each patient constitutes an individual problem and the diet must be adjusted according to the conditions present. Detailed diets may be found in the many excellent books on nutrition and dietetics. In cases where there is disturbance of gastric function, rectal feeding becomes of some value and intravenous feeding may be successfully carried on for short periods of time.



## EMERGENCY MANAGEMENT IN THE CRISES OF HEART DISEASE

A. CARLTON ERNSTENE

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SITUATIONS in which the prompt institution of proper treatment may be directly responsible for the saving of life probably are encountered more frequently in patients with organic heart disease than in any other group of individuals. A thorough understanding of the therapeutic measures available for use in patients critically ill with heart disease therefore is of considerable importance. Fortunately, practically all of the measures of established value are of such simple nature that one can easily be prepared to use them at all times.

### ADVANCED CONGESTIVE HEART FAILURE

It happens not infrequently that a patient with congestive heart failure is first seen only after his condition has become critical. Usually, under these circumstances, the patient has experienced increasingly severe symptoms for days or even weeks. Examination reveals an exhausted, apprehensive individual in extreme respiratory discomfort, with orthopnea, cyanosis, engorgement of the jugular veins, an enlarged, tender liver and extensive peripheral edema. Hydrothorax and ascites may be present, and in many patients there is repeated vomiting. The cardiac rhythm may be regular or irregular; the most common type of arrhythmia observed is auricular fibrillation with a very rapid ventricular rate and a large radial pulse deficit.

In situations of this kind, the first indication is for the administration of digitalis. Because a delay of even a few



hours in obtaining the therapeutic effect of the drug may mean a fatal outcome, intravenous administration is necessary. It is important to bear in mind in this connection that when digitalis action is urgently needed, one must not rely upon intramuscular injection, and particularly is this true in the edematous patient. There are several preparations of digitalis on the market which are put up in ampules for intravenous use. Unfortunately, these preparations differ considerably in potency among themselves and, to a somewhat lesser extent, in different lots of the same product.<sup>1</sup> It therefore is advisable that one become familiar with the clinical action of a single preparation and confine himself to the use of that preparation. For most of the products on the market, an initial intravenous dose of 6 cc. is suitable, and the same dose can be repeated, if necessary, after an interval of four hours. After this, it is generally advisable to complete the process of digitalization either by oral administration of the drug, if vomiting has ceased, or by intramuscular injection.

If one prefers, strophanthin may be given intravenously in place of one of the digitalis preparations. This drug, however, possesses no definite advantages over digitalis and is dangerous when given in large doses. When used, the initial dose should be not more than 0.5 mg. Additional doses of 0.1 mg. may be given if necessary at intervals of four hours until a total of not more than 1 mg. has been administered. It is, of course, important to ascertain that patients to whom digitalis or strophanthin is given intravenously have not received digitalis within the preceding two weeks.

The intravenous administration of digitalis or strophanthin may produce remarkably prompt improvement in the patient who is critically ill with congestive heart failure, and particularly is this true when auricular fibrillation is present. In patients with auricular fibrillation, slowing of the ventricular rate usually is noted within five minutes after administration of the drug, and within one half hour there may be complete cessation of vomiting and great diminution in the degree of dyspnea. Strophanthin attains its maximum effect in approxi-

mately one hour and the digitalis preparations in about two hours after intravenous injection.

In addition to receiving digitalis or strophanthin intravenously, patients who are desperately ill with congestive heart failure should be given morphine sulphate immediately by hypodermic injection. The drug depresses the respiratory and vasomotor centers in the medulla as well as the higher cerebral centers, and by so doing, relieves the patient's dyspnea and his anxiety and apprehension. Not only should morphine be administered when the patient is first seen, but a second injection, usually of  $\frac{1}{4}$  grain, should be given the same evening to insure a comfortable night's rest. Several hours' sleep frequently results in striking improvement in the general condition and morale of the patient.

Advanced congestive failure often is attended by the accumulation of large amounts of fluid in the serous cavities of the body. Extensive hydrothorax may be present on one or both sides and, by compressing the lung, may be responsible for a considerable part of the patient's reduction in vital capacity and resultant dyspnea. It therefore is important that the fluid be removed as completely as possible soon after the initial administration of digitalis and morphine. Less frequently, ascites is present in sufficient amounts to interfere with the movements of the diaphragm and thus contribute to the degree of dyspnea. Under such circumstances, abdominal paracentesis is indicated.

In patients with myocardial failure, the peripheral venous pressure is increased roughly in proportion to the degree of decompensation. In the presence of severe failure, the jugular veins may be engorged to the angle of the jaw even with the patient well propped up in bed. Venesection with the removal of from 250 to 500 cc. of blood may result in prompt improvement in cases of this kind and should be employed whenever the institution of digitalis therapy and other measures discussed above fail to produce satisfactory improvement. This procedure directly reduces venous congestion and diminishes the degree of dilatation of the heart. It is desirable to make

measurements of the venous pressure during the removal of the blood and to continue the bleeding until the pressure has been reduced to within the upper limits of normal. For practical purposes, however, a reliable guide is furnished by observations on the jugular veins, venesection being continued until jugular distention has been relieved. In favorable cases, the venous pressure remains low after having been reduced by venesection, whereas in unfavorable cases a more or less prompt return of peripheral venous congestion occurs.

#### ACUTE CORONARY ARTERY OCCLUSION

The clinical picture of sudden occlusion of a branch of the coronary arteries is too well known to require further detailed description. The condition constitutes one of the most important crises of heart disease, and the first aim in its treatment is relief of the pain. For this purpose morphine should be given promptly and, if necessary, in repeated doses. The initial dose of the drug usually should be  $\frac{1}{4}$  grain hypodermically, and subsequent injections of the same amount should be given at intervals of twenty to thirty minutes until the patient becomes comfortable. If an oxygen tent is available, the patient should be placed in it, since oxygen therapy frequently is helpful in shortening the duration of the pain and in relieving dyspnea and cyanosis. Nitroglycerin should not be administered, for it will have no effect upon the pain and, by reducing blood pressure, it may further embarrass the coronary circulation. Coronary occlusion occasionally results in the rapid development of a state of profound shock with loss of consciousness. Under such circumstances, the intramuscular administration of 0.25 to 1.0 cc. of a 1:1000 solution of epinephrine hydrochloride or of 0.5 Gm. (7.5 grains) of caffeine sodium benzoate may be a life-saving procedure. The patient should, of course, be kept warm, and all unnecessary movement should be avoided. At a later period, measures may be necessary for support of the circulation or for the control of auricular fibrillation or ventricular paroxysmal tachycardia.

## CARDIAC ASTHMA AND ACUTE PULMONARY EDEMA

Cardiac asthma is a form of paroxysmal dyspnea which occurs in patients with serious organic heart disease. Occasionally, its onset gives the first warning of the presence of a damaged heart, although more often the patient has experienced dyspnea or anginal pain on effort for some time before the first seizure. The attacks develop rapidly and are characterized by asthmatic breathing with both inspiratory and expiratory difficulty, orthopnea and a sense of suffocation. The paroxysm may last from several minutes to a few hours and may progress to acute pulmonary edema with frothy, blood-tinged sputum. Death may occur during the attack.

In the great majority of cases, cardiac asthma is due to failure of the left ventricle, which has been damaged previously as the result of hypertension, coronary artery sclerosis or aortic valve disease. The seizures in these cases usually occur at night, although occasionally they are induced by exertion. In a much smaller group of patients the attacks result from the presence of advanced mitral stenosis without myocardial failure. A series of such cases has been studied by McGinn and White,<sup>2</sup> who point out that, in contrast to attacks resulting from failure of the left ventricle, cardiac asthma in patients with uncomplicated mitral stenosis usually is precipitated by exertion, emotional upsets or paroxysmal tachycardia. When the heart rate is accelerated by any of these factors, the hypertrophied right ventricle expels blood into the pulmonary circulation more rapidly than it can pass through the narrowed mitral orifice. Acute pulmonary congestion develops and results in a paroxysm of cardiac asthma.

The two most effective measures in the treatment of attacks of cardiac asthma are morphine and the upright position. Morphine should be administered hypodermically as early in the attack as possible, usually in doses of  $\frac{1}{4}$  grain, and should be repeated if the patient does not appear improved within fifteen or twenty minutes. Cardiac asthma is attended characteristically by orthopnea. At the onset of a paroxysm the patient is forced to assume a sitting or standing

position and frequently supports himself with his arms against a chair, table or windowsill. It is probable that the increase in vital capacity which accompanies the change from the recumbent to the erect posture contributes importantly to the relief experienced in the latter position.

Morphine and the upright position may at times fail to relieve the patient sufficiently, and other measures must then be employed. In the absence of anemia, venesection should be carried out with the removal of from 250 to 500 cc. of blood. This may result in prompt and lasting relief, particularly in patients who present engorgement of the peripheral veins. Weiss and Robb<sup>3</sup> have observed that an effect similar to that of venesection, and often more prompt and lasting, may be obtained by applying blood pressure cuffs to the four extremities and inflating them to a pressure just above diastolic blood pressure.

In patients in whom cardiac asthma progresses to acute pulmonary edema in spite of these measures, digitalis or strophanthin should be administered intravenously in the dosages previously outlined. It is, of course, essential to ascertain that these patients have not received digitalis earlier.

#### PERICARDIAL EFFUSION

In the majority of cases of pericardial effusion, the amount of fluid present is not sufficiently large to embarrass the circulation importantly, and pericardial paracentesis is not necessary. Occasionally, however, an effusion becomes so extensive that the superior and inferior venae cavae are compressed and the return flow of blood into the right auricle is interfered with. Unless this excessive intrapericardial pressure is relieved, the condition may prove rapidly fatal. The most important indications that a pericardial effusion is attaining dangerous proportions consist of severe orthopnea, cyanosis, greatly elevated venous pressure and a rapid fall in arterial blood pressure with a small pulse pressure. The development of these symptoms and signs calls for paracentesis with the removal of as much fluid as is possible without producing pain,

cough or faintness. The procedure is carried out under novocain anesthesia, and the needle usually is introduced either in the left fifth intercostal space just within the outer border of dulness or in the right fourth intercostal space just inside the right border of dulness.

#### VENTRICULAR PAROXYSMAL TACHYCARDIA

Ventricular paroxysmal tachycardia is a relatively rare condition which is almost always due to the presence of serious organic heart disease. It occurs most commonly as a complication of coronary thrombosis and may be the forerunner of ventricular fibrillation. The paroxysm frequently is attended by serious collapse and occasionally by the rapid development of acute pulmonary edema. Levine<sup>4</sup> has pointed out that it is possible to recognize this type of tachycardia by clinical means alone in a large proportion of the cases. Carotid sinus or ocular pressure has no effect upon the heart rate in this condition in contrast to the effect of these procedures in auricular paroxysmal tachycardia and auricular flutter. Furthermore, if one listens carefully to the heart, an occasional slight irregularity in rhythm will be noted, and in addition the intensity of the first heart sound will vary from time to time. The one drug of established value in the treatment of this type of tachycardia is quinidine sulphate administered by mouth. Usually, an initial dose of 3 grains is given, and this is followed at intervals of two hours by additional doses of 6 grains each until a total of not more than 6 doses has been administered. Morphine may be necessary for the relief of dyspnea, while the occurrence of acute pulmonary edema calls for the administration of oxygen.

#### ADAMS-STOKES SYNDROME

Ventricular standstill resulting from high-grade heart block and causing faintness, syncope and convulsions is a rare condition. Usually the seizures are of such short duration that treatment is directed toward prevention of their recurrence rather than toward relief of the actual attack. For this pur-

pose, the two most useful drugs are epinephrine hydrochloride administered subcutaneously or intramuscularly every few hours in doses of 0.25 to 1.0 cc. of the 1: 1000 solution, and ephedrine sulphate by mouth in doses of  $\frac{3}{8}$  grain three or four times a day. Very rarely indeed, one may actually witness a prolonged period of ventricular standstill accompanied by unconsciousness and convulsions. The intracardiac injection of epinephrine hydrochloride (0.25 to 1.0 cc. of 1: 1000 solution) is indicated under such circumstances and may be a life-saving procedure.

### CONCLUSION

The conditions which have been discussed comprise the most important of the emergencies of heart disease for which effective therapy is available. The diagnosis of these conditions is for the most part simple and certain; and if one is prepared to carry out the recommended therapeutic measures, he will not infrequently witness the recovery of a patient who at first sight seems hopelessly ill.

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## DIAGNOSIS AND TREATMENT OF ESSENTIAL HYPERTENSION

R. H. McDONALD

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NORMAL blood pressure depends upon the two chief factors of the energy of the contracting ventricle and the resistance offered by the peripheral circulation. The former factor is operative only during the time the aortic valves are open, while the latter is present during the whole cardiac cycle. The latter depends partially upon the elastic recoil of the arterial walls and partially upon the state of contraction of the muscular elements of the vascular system. Both factors are controlled by the autonomic nervous system and are subject to variations in nervous control in response to stimulation from the cerebral cortex or reflexly from any other portion of the nervous system. The height of the blood pressure therefore, at any given moment, is dependent upon nervous control and can be varied in very short periods of time in order to maintain an efficient circulation under any condition. This flexibility of the blood pressure allows a wide range of readings in the normal individual. Under the stimulus of heavy muscular exercise or severe mental stimulation, the normal individual may have increased blood pressure readings which fall rapidly when the excessive stimulus is removed. In this connection, it is well to remember that single elevated pressure readings do not establish a diagnosis of hypertension. Even the mental stimulus of physical examination in the apprehensive individual may elevate the pressure well above the basic level. The initial readings in such persons are therefore almost invariably too high, and for this reason, the blood pressure reading should not be done until the physical examination has progressed to a point where the patient has become accustomed to his sur-



roundings, and when his confidence has been obtained. In this respect, the blood pressure reading corresponds to the estimation of the basal metabolic rate which would never be credited if it were not done under conditions which precluded, as far as possible, external stimulation. We are interested in determining the basal blood pressure, not the measure of response which occurs under stimulation, which is merely an index of the irritability of the autonomic nervous system. This latter depends upon the nervous stability of each individual and is often a constitutional factor of an inherited type. It is probably true that those individuals who have an unstable autonomic system are potential candidates for fixed hypertension, but great care must be exercised in estimating the significance of the blood pressure readings in such individuals. One patient of apprehensive type who was seen by the writer, was found on routine physical examination to have a pressure of 240 systolic, 120 diastolic when she was admitted to the hospital for herniotomy. Operation was deferred and the following day the pressure was 160 systolic, 100 diastolic. The next morning the pressure was 140 systolic, 80 diastolic. Operation was performed, and during the remainder of the hospital stay the pressure did not rise above 130 systolic, 80 diastolic. Two years later the pressure was again found to be entirely normal, although there was still considerable variability in the readings.

Minor factors concerned in the maintenance of the blood pressure are the blood volume and its viscosity. These purely physical factors are relatively stable and show variability only during severe constitutional disturbances.

In general, the hypertensive patients fall into two main classes: those in whom the hypertension is an accompaniment or sequence of a primary renal lesion, and those in whom the hypertension develops independently of any renal lesion which can be detected or, in fact, independently of any detectable organic disease. The latter group constitutes the so-called "essential" hypertension and perhaps includes a variety of conditions which have the common characteristics of arterial

hypertension rather than a single entity. It is unfortunate that a definition of essential hypertension must be set forth in terms of what it is not, but in the present state of uncertainty of the basic etiological factor, this is the only alternative. Nonrenal hypertension of known etiology is usually not included with essential hypertension. Thus, the increased blood pressure resulting from increased intracranial pressure which appears obviously to be a reflex designed to maintain an efficient cerebral circulation, is excluded as well as the paroxysmal hypertension seen in tumors of the adrenal cortex.

The early clinical diagnosis of hypertension depends upon the routine use of the sphygmomanometer with repeated readings if necessary and careful clinical evaluation of the result. Frequently, hypertension is diagnosed by this means only, in the entire absence of symptoms or signs, and thus its use is absolutely essential. The earliest clinical symptoms may be very indefinite and suggestive only of vasomotor instability so that they may be regarded as of purely functional origin. Symptoms of disturbance of the cerebral circulation, headache, dizziness, vertigo, insomnia, and inability to concentrate are frequently encountered in the individual whose work is chiefly mental, whereas in the laborer, dyspnea on exertion, palpitation, precordial distress and other evidences of cardiac embarrassment may be the initial complaints. Evidences of renal deterioration are rarely seen as initial symptoms, inasmuch as the renal degeneration is secondary to the vascular change accompanying the hypertension and this develops relatively slowly.

In many instances the presence of hypertension is only detected when a sudden circulatory disturbance impairs the function of heart or brain to such an extent that the patient is driven to seek advice. An attack of angina pectoris or a coronary thrombosis may occur in an otherwise symptom-free individual and indicate the presence of an unsuspected hypertension. Transient cerebral spasms associated with temporary paralysis, transitory aphasia or other mental upsets may call attention to the instability of cerebral circulation. Apoplexy

is frequently the initial symptom. Sudden amaurosis or other visual disturbances have been noted. Circulatory disturbances in the extremities in the form of paresthesias or even intermittent claudication are sometimes seen. Epistaxis, hemoptysis, and gastro-intestinal hemorrhage are rare complications of essential hypertension in its initial stages.

The differentiation between the renal and nonrenal types of hypertension may usually be made after a careful consideration of the history, physical examination, and certain laboratory findings. The patient with chronic hemorrhagic Bright's disease usually gives a history of an acute phase with gross urinary changes and edema or relates the onset of his difficulty to some acute infection suggestive of a streptococcal invasion. In the vast majority of essential hypertensives there is no definite starting point but an insidious development of certain symptoms which at last have culminated in a vascular accident or have been explained by routine physical examination. The elevation of blood pressure and the resultant cardiac hypertrophy is generally greater in the patients with essential hypertension and the general condition is usually much better. Anemia is much less marked in this group; urinalysis may be entirely normal at first or show only small amounts of albumin with a few scattered blood cells and casts whereas in chronic Bright's disease, there is constant urinary evidence of severe renal deterioration, which is especially evidenced by the presence of red blood cells. This difference is frequently striking when the renal reserve is measured by the *urea clearance test*.

The vascular reactions in essential hypertension have been studied extensively and evidences of increased vasomotor irritability have frequently been noted following deep inspiration, thermal stimulation, pressure on the eyeball or carotid sinus. The injection of histamine intradermally in essential hypertensives has been found to produce a much smaller "flare" than in the normal individual. Examination of the retina is of little practical importance in the differentiation of the two types of hypertension inasmuch as the vascular changes are

not in themselves characteristic in either case, but are apparently largely the result of increased pressure *per se*.

The marked frequency with which the physician is confronted with the problem of hypertension makes it a therapeutic problem quite comparable to that of malignant disease. In fact, from the purely economic point of view, it would seem that the problem is of more importance inasmuch as the great majority of severe hypertensives suffer disability in their productive years, whereas the majority of victims of malignant disease have passed their peak. It is rather interesting to note, however, that in neither the medical nor the lay mind has the problem been accorded anything approximating the study or importance accorded to malignancy.

Naturally, the purpose of any prescribed treatment would be to eradicate the cause of the disturbed circulatory dynamics since, obviously, the hypertension in itself is merely a symptom of some derangement of function. It seems fairly well established that the immediate cause of the hypertension is an increase in the peripheral resistance, a hypertonus of the vascular musculature associated with an extreme and sustained vasoconstrictor nervous impulse, the consequence of which over a period of time is vascular damage. At the present time, it appears that several causes or conditions may contribute to this state and therapy must, therefore, be devised to suit the requirements in the individual case.

Specific therapy in the present uncertain state of our knowledge is not feasible, and we must await further elucidation of the exact functional disturbance before such measures can be utilized. However, the medical profession must guard against the adoption of a too pessimistic attitude with regard to this condition. Much can be done to alleviate the symptoms and to assist in combating the various manifestations and complications of the disease. It is true that there appears to be no record of cure in any clear-cut case of essential hypertension, but on the other hand, one frequently sees patients with severe hypertension who have carried on for many years.

The prevalence of the disease and the striking nature of its

complications and sequelae have been responsible for the development of a phobia of hypertension which in itself aggravates the basal condition. The physician who has taken time to appraise his patient's lesion accurately and in so doing has established himself in his patient's confidence, may greatly help the mental peace and quietude by a frank discussion of the problem, although in general it is best to refrain from telling him the exact level of his blood pressure. Many individuals are apt to attach great importance to the exact mathematical readings and to variations of these reading at different times. The adoption of a quiet routine of life and the education of the patient to a schooled inward calm are intangible factors of the greatest importance, although admittedly, these may be difficult to attain under present economic and social conditions. Moderation in all the activities of life should be emphasized, in physical exertion in the individual of strenuous type and in mental effort in those who are accustomed to overdo in this respect. Moderation in regard to eating is essential and in the plethoric type of individual, the reduction of excessive weight will frequently be accompanied by a gratifying reduction in the blood pressure. Adequate and frequent rest and careful avoidance of an exhaustion state will often reduce the pressure below the dangerous limits, and the value of regular vacations should be stressed. Excessive heat and humidity have been shown to increase pressure and are generally poorly tolerated by patients with hypertension. Moderate exercise may be tolerated well, but the functional state of the heart should be considered.

A great deal has been written on the dietary management of increased blood pressure, but it still remains to be proved that any special diet exerts a specifically beneficial effect. Caloric restriction in the obese patient has proved of value, but the diet should be varied and it should be adequate to prevent deficiencies which are becoming more and more obvious in many of the patients who adhere to dietary fads. Especially has it been proved that the older idea of protein restriction is untenable and in itself the basis for secondary symptoms

of general weakness and anemia. A moderate intake of protein sufficient at least to maintain the nitrogen equilibrium is essential. The type of protein food is of less importance than its adequacy, and the old popular idea of the necessity of barring the red meats has no justification. Renal insufficiency in cases of arteriosclerotic renal disease, as evidenced by increased nonprotein blood values of renal origin, necessitates a lowered protein intake. Restriction of fluid intake seems justifiable only in instances of myocardial weakness and failure, but there seems no reason for forcing the ingestion of very large amounts of fluid on the theory of flushing out hypothetical toxins. Moderate restriction of sodium chloride is usually advised, but enough is allowed to make the food palatable. The use of condiments and highly spiced foods should be prohibited. It is generally agreed that the use of tea and coffee should be restricted and that the use of alcohol and tobacco should be reduced to moderate levels in those patients who feel that their absolute prohibition constitutes a hardship.

The multiplicity of drugs suggested and used in the treatment of hypertension is eloquent evidence of the regrettable fact that all fall short of anything approaching a specific effect. Probably, the drug therapy most used is some form of nitrite such as amyl nitrite by inhalation which is the quickest in action although most evanescent in effect,  $\frac{1}{100}$  grain of nitroglycerin, which is less rapidly active but more sustained in effect, 1 or 2 grains of sodium nitrite which is still slower in action but has a more prolonged effect. From  $\frac{1}{2}$  to 1 grain of erythrol tetranitrate is again slower in action but with still more prolonged effect. Its action depends upon the formation of nitrite within the body, the nitrite in this case as in each of the above substances, acting by a peripheral vasodilation, the effect being either directly upon the smooth muscle of the arterioles or upon the sympathetic myoneural junction. More recently, an attempt has been made to prolong the effect of vasodilation by the use of bismuth subnitrate in capsules of 10 grains each which are given by mouth. The slow decomposition of the nitrate to nitrite by the action of intestinal

bacteria theoretically provides a prolonged source of medication. It has never been established that the use of the nitrites offers any more than temporary symptomatic relief, but these undoubtedly increase the comfort of certain patients and are especially valuable in combating symptoms secondary to periodic elevations of pressure, notably anginal attacks and the transient cerebral phenomena associated with cerebral vascular spasm. It is frequently observed, however, that the sudden reduction of hypertension by the nitrites results in discomfort and evidences of insufficient cerebral circulation, especially in arteriosclerotic patients.

Iodides in minute concentration have been regarded as vasodilators, but clinically they appear to be useful only in certain cases because of their alterative action. Calcium salts have been recommended on theoretical grounds but clinically are of little value. Sulphocyanates and thiocyanates have been widely used and in a few cases seem to cause subjective improvement and are effectual in some reduction of pressure. However, toxic symptoms such as exfoliative dermatitis or symptoms referable to the cerebral cortex have militated against their more widespread use. I have found the purine derivatives, theobromine and theophylline in various forms, to be useful in securing considerable subjective relief, although it appears certain that no consistent manometric success may be expected from their use. Mild sedatives, either alone or in combination with some of the above therapeutic agents, have certainly helped greatly in the treatment of patients with these difficult problems. Especially is this true in the patient who displays marked sympathetic hypersensitivity. Bromides and barbituric acid derivatives appear most suitable for prolonged administration, but for emergency use, codeine and various forms of opium may be necessary.

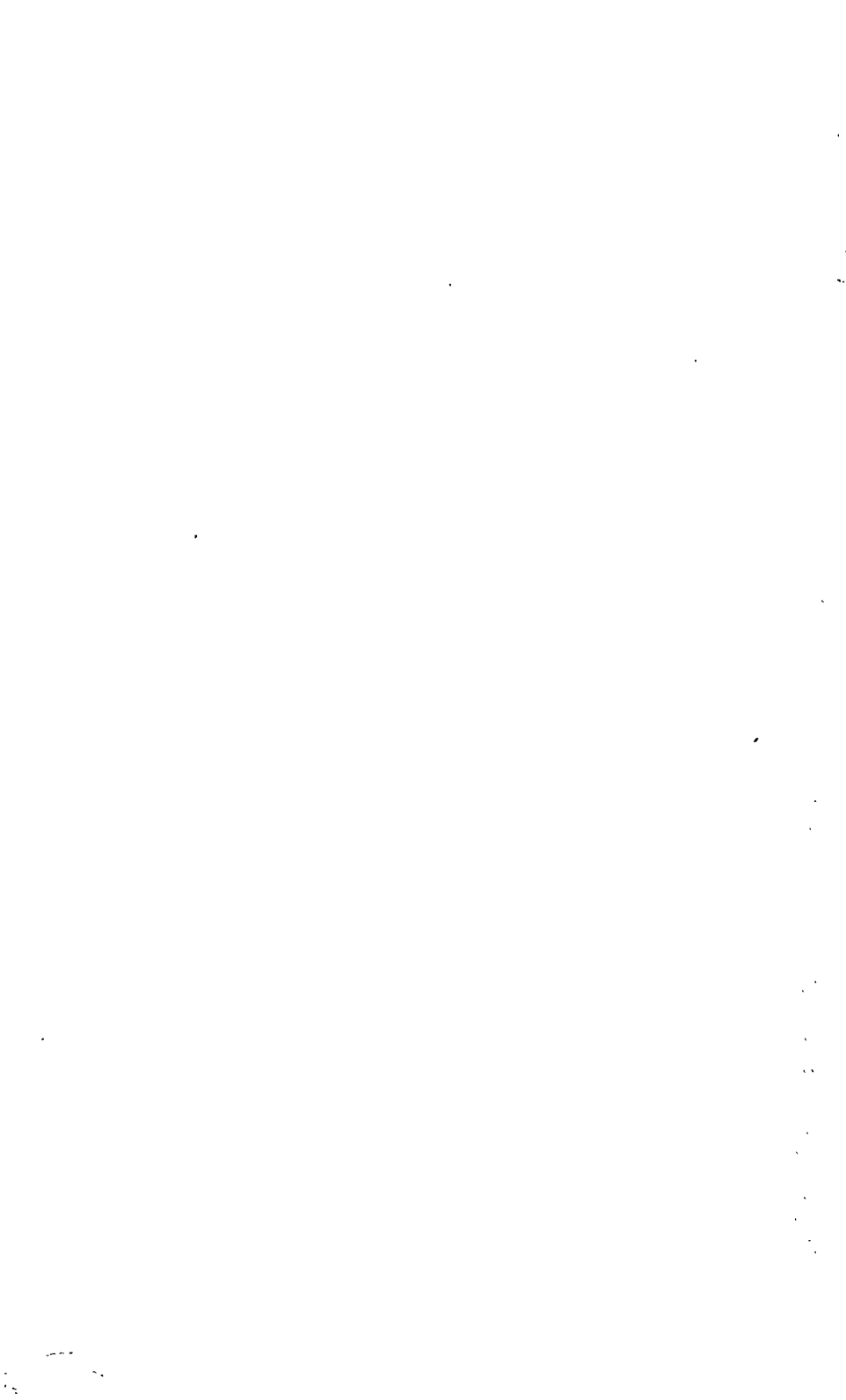
The literature contains numerous articles which record some degree of success with many other preparations. The use of liver extract failed to justify the earlier hope that this would prove to be an effective method of treatment. Benzyl benzoate has been used and more recently an extract of watermelon seed has been accorded some therapeutic virtue. For the most

part, organotherapy has been disappointing, but the use of ovarian hormone has been distinctly useful in those cases of hypertension associated with the menopause. The use of the high-frequency current and diathermy has found support by some observers, but the effect is limited. Vigorous physiotherapy, massage and warm baths should be used with care.

The failure of the physician to produce a cure has drawn the surgeon into the problem and in recent years, a considerable literature has accumulated on the subject of operative intervention. In general, the theory underlying the surgical attack is the relief of vasoconstriction by cutting the sympathetic nerves which supply the splanchnic area, thus preventing constriction of a considerable fraction of the vascular bed and providing a sort of safety valve. It is also argued that such a procedure prevents renal vasoconstriction and good experimental evidence has been presented that narrowing of the renal vascular supply will cause a general increase in blood pressure. Further, it is argued that such a measure will decrease adrenalin production. However, it has never been proved that ordinary hypertension is due in any way to increased adrenalin production although there are well proved instances of paroxysmal hypertension associated with adrenal tumors. Denervation of the adrenal glands has been performed either alone or with splanchnic section in the hope of reducing the sympathetic vasoconstrictor impulse. Some favorable results have been reported from these surgical procedures, but success has been only partial in the majority of cases and lacking in others.

The whole question of the etiology of essential hypertension requires further elucidation before a more logical therapy can be expected. It constitutes a problem of tremendous economic importance and merits the careful study and consideration of the medical profession in order that the resultant disability and discomfort may be relieved. In the meantime, the careful clinician must continue to study these patients individually, and use every method at his disposal for their comfort and relief.





## REMARKS ON A FEW COMMON SKIN ERUPTIONS SEEN FREQUENTLY DURING THE SUMMER MONTHS

E. W. NETHERTON

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IN discussing the increased seasonal incidence of certain common dermatoses, we are in reality referring to the degree of exposure of the population to environmental hazards during certain months of the year. The degree of exposure to common hazards will naturally be influenced by the climate, geographical location, occupation, clothing, and the types of recreation of an individual. In the semitropical climates of some of the southern states, the inhabitants are not subjected to the seasonal changes in temperature which necessitate a modification of clothing or which result in changes in recreational activities such as are the people who live in the northern or temperate climates. Therefore, the incidence of common dermatoses in the South should not vary a great deal. However, in the temperate climates with the advent of the summer months, people of the cities emerge from a relatively sedentary life to engage in their favorite outdoor recreation such as golf, swimming, picnicking, fishing, etc., while those in the rural communities become actively engaged in outdoor occupations such as farming and gardening. At this time of the year, an individual wears less clothing and perspires freely; a larger portion of his body is exposed to intense sunshine; he is frequently bitten by insects and frequently comes in contact with many types of vegetation. Therefore dermatitis venenata, fungal infections, insect bites with secondary infection and cutaneous eruptions resulting from increased perspiration and the deleterious effect of excessive heat and ultraviolet rays are especially common at this time of the year.

Some of the common dermatoses whose incidence is influenced by the factors just mentioned are:

1. Those resulting from exposure to intense sunshine.
  - (a) Erythema or dermatitis solare (sunburn).
  - (b) Lentilles or freckles.
2. Those resulting from intense heat and increased perspiration.
  - (a) Miliaria crystallina. Heat rash or prickly heat.
  - (b) Intertrigo.
3. Insect bites—browntail moth dermatitis.
4. Dermatitis venenata resulting from contact with plants or their pollens, bathing suit dermatitis, etc.
5. Parasitic infections.

The deleterious effect of sunlight on the skin is produced by the actinic or ultraviolet rays, rather than by the heat rays. This is the same biologic reaction which is produced by modern actinotherapy. Individuals with delicate skins and fair complexions are especially susceptible to the injurious effects of the actinic ray. The objective signs appear a few hours after exposure. The face, neck, upper portions of the trunk or the parts of the body most frequently exposed are the areas of predilection. There is first a sensation of smarting and itching followed in a short time by erythema and edema. In cases of severe and extensive sunburn, there is marked edema with vesicular and bullous lesions and associated constitutional symptoms such as general malaise, temporarily impaired kidney function and edema of the lower extremities. As the acute cutaneous reaction subsides, desquamation occurs and a variable degree of pigmentation results which tends to protect the individual from subsequent exposure to the actinic rays. Superficial scarring sometimes occurs in severe cases.

In some individuals small pigmented macules or freckles are particularly prone to develop on the face and dorsum of the hands when they are exposed to sunlight. Macleod<sup>1</sup> states that these individuals do not readily become sunburned. Ordinarily, the freckles decrease in number during the winter months; however, in localities where the winter days are clear

and the snow plentiful, both sunburn or dermatitis solare and freckles may result from the reflection of the actinic rays by the snow.

Although this discussion is concerned mainly with common conditions, three other dermatoses should be mentioned: these are xeroderma pigmentosum, hydroa vacciniforme, and lupus erythematosus. These conditions are sometimes referred to as light sensitive dermatoses. The exact mechanism of their causation is unknown; however, it is known that the actinic ray of sunshine will precipitate an attack of hydroa or aggravate a xeroderma pigmentosum. In the past many observers have felt that probably some photosensitive substance in the blood, such as the porphyrins, was an important factor in the causation of these dermatoses. More recent reports do not verify this opinion. Templeton and Lunsford<sup>2</sup> were able to produce porphyrinuria in patients not sensitive to light by exposure to ultraviolet light and have observed porphyrinuria in patients suffering from dermatoses which were not due to light sensitization. Likewise, porphyrinuria is present in only a small percentage of the patients with light sensitive dermatoses. In an excellent article, Anderson and Ayres<sup>3</sup> have recently reviewed the literature and discussed the problem of light sensitive dermatoses. They submit evidence which they believe points to a disturbed sulphur metabolism as a factor in the production of light sensitization.

Xeroderma pigmentosum is a rare disease with a familial tendency. It appears early in life, starting as freckle-like pigmentation with white atrophic areas and telangiectasia. As the disease progresses, warty growths, ulceration and finally carcinoma develop, and death occurs usually before the patient reaches adult life.

Hydroa vacciniforme is also a rare condition. It is characterized by a recurrent papular, or papulovesicular eruption occurring on the face, neck, back, hands and forearms. In severe cases, bullae and superficial ulcers occur. After repeated attacks which occur during the summer months, scarring results.

Lupus erythematosus which is characterized by well-defined, persistent erythematous, scaly plaques, which show enlarged plugged follicles and subsequent central atrophic scarring, occasionally makes its initial appearance following a sunburn. It may be considered as one of the sequelae of sunburn. Because of this, it is unwise and unsafe to treat this condition with actinotherapy.

The treatment of sunburn or dermatitis solare is symptomatic. In the acute erythematous stage without vesiculation, a cool evaporating and protective lotion or powder should be used. Creams and ointments are not satisfactory and add to the discomfort of the patient because they prevent radiation of the heat from the acutely inflamed tissues. The well-known calamine lotion with 1 per cent phenol is a very satisfactory preparation or the following powder is useful:

R <sub>x</sub>	Gm. vel cc.
Thymol.....	7
Pulv. boric acid.....	60
Pulv. starch.....	30
Talcum.....	q. s. ad 120
M. and ft. pulv.	

If vesiculation has occurred, the vesicles should be drained using aseptic precautions and a moist dressing of Burrow's solution, 1 part to 12 or 15 parts of water should be applied. In severe cases, the patient should be confined to bed. After the acute stage has subsided and desquamation has started, a bland ointment such as the following is indicated:

R <sub>x</sub>	Gm. vel cc.
Phenol.....	3
Zinc oxide.....	8
Pulv. starch.....	8
Cold cream.....	10
Vaseline.....	q. s. ad 30
M. and ft. ung.	

Various commercial preparations are offered to the public for the prevention of sunburn, but many are of doubtful

value. Various drugs which have been considered to absorb the ultraviolet rays have been incorporated in creams and applied to prevent sunburn. Quinine is one of the most commonly used drugs. Salsberg<sup>4</sup> has found the following preparation very satisfactory for the prevention of sunburn:

R	Gm. vel cc.
Quinine hydrochloride. . . . .	18
Zinc oxide. . . . .	6
Glycerine. . . . .	12
Rose water. . . . .	120
M. and ft. lot.	

Sharlit<sup>5</sup> recommends phenyl salicylate (salol) in 10 per cent strength incorporated in cold cream. This cream is applied in a thin layer.

Miliaria crystalline commonly called heat rash or prickly heat is due to excessive heat; consequently it is most prevalent during hot weather. It is seen particularly in infants who are clothed too warmly. Heavy woolen underwear, overeating, and violent exercise with profuse perspiration contribute to its causation. Obese individuals or those whose occupation necessitates their exposure to high temperatures such as bakers and cooks are especially prone to have miliaria. This eruption is not a serious one but in severe cases, the itching and burning sensations are especially troublesome in the early stage of the eruption. The eruption is characterized by very small, pointed or conical papules many of which develop a small vesicle at the apices. There are also small vesicles on erythematous bases scattered throughout the eruption. The lesions occur in clusters, are very numerous and remain discrete. The papules are seldom larger than a large pinhead. In order to observe the characteristics of the individual lesions, the eruption must be examined by a magnifying lens. The onset of the eruption is preceded by profuse perspiration and is accompanied by itching and burning of varying severity. The wrist line, thighs, upper portion of the trunk, and neck are the areas most frequently involved. Severe cases may become

complicated by impetigo, pyodermia or eczematization as a result of scratching.

The management of miliaria is not a complicated problem provided the patient can avoid exposure to excessive heat and perspiration. The underclothing should be light, preferably of cotton; the diet should not exceed the needs of the patient; and the body should be kept clean by a daily bath. In severe cases the bath should be of an alkaline type. This is prepared by adding 4 ounces of sodium bicarbonate and a paste made with water and  $\frac{1}{2}$  pound of corn starch to a bath tub of average size half full of lukewarm water. Instead of this soda and starch mixture, 20 grains of potassium permanganate may be added to the bath. Following the bath the following lotion will usually be beneficial,

R <sub>x</sub>	Gm. vel cc.
Phenol. . . . .	1   2
Prep. calamine. . . . .	8
Zinc oxide. . . . .	8
Glycerine. . . . .	3
Rose water. . . . .	q. s. ad 120
M. and ft. lot.	

or a powder such as,

R <sub>x</sub>	Gm. vel cc.
Salicylic acid. . . . .	2   4
Pulv. boric acid. . . . .	40
Pulv. zinc oxide. . . . .	40
Talcum. . . . .	q. s. ad 120
M. and ft. pulv.	

If there is a secondary pyoderma or a tendency to the development of furuncles which are more frequently seen in infants, potassium permanganate should be used in the form of baths or in the form of moist packs in 1:10,000 solution followed by an application of a 2 to 5 per cent ammoniated mercury ointment. The anointed surface should then be dusted with borated talcum.

Intertrigo is a term used to designate the erythema or der-

matitis which results from the friction of two opposing cutaneous surfaces. It occurs most commonly on the inner surface of the thighs, in the gluteal fold, in folds of the abdomen or under pendulous breasts. The friction and excessive sweating of contiguous surfaces are the most important exciting factors. Uncleanliness as well as too frequent use of irritating soaps for bathing contribute to the causation of intertrigo. As would be expected, the condition is more prevalent in obese individuals. Intertrigo of the thighs is occasionally associated with diabetic vulvitis.

In adults, intertrigo involving the inner surfaces of the thighs must not be confused with an epidermophyton infection. In intertrigo the eruption is definitely symmetrical, it is not sharply marginate and the borders are not obicular as in the case of epidermophyton infection. In doubtful cases, a search should be made for fungi in the scales taken from the lesions.

A condition which some of the earlier authorities classified as a type of intertrigo involves the gluteal folds and adjacent surfaces of the buttocks of infants; this is sometimes called Jacquet's dermatitis which must be differentiated from congenital syphilis. The lesions of congenital syphilis are of a darker color, are slightly infiltrated and are associated with other signs of congenital syphilis. If moist lesions are present, a dark-field examination should be made for the spirochete especially in cases where the diagnosis is doubtful.

Cleanliness with a minimum of irritation or trauma of the affected surfaces is of prime importance in the treatment of intertrigo. Ointments tend to increase the maceration of the epidermis, consequently lotions and dusting powders are most acceptable. The powder and lotion advised in miliaria will be especially valuable in intertrigo. Occasionally, the skin may become lichenified after the more acute phase of intertrigo has subsided. In such cases the use of a mildly stimulating and antipruritic ointment is indicated. The following is recommended:



R	Gm. vel cc.
Ung. picis lig.....	4
Salicylic acid.....	1
Pulv. zinc oxide.....	4
Pulv. starch.....	8
Ung. diachylon.....	4
Vas. alb.....	q. s. ad 30
M. and ft. ung.	

Cooke<sup>6</sup> has demonstrated that the bacterial production of ammonia is the important etiological factor in the production of the dermatitis of the gluteal fold in infants which is often considered as an intertrigo. He found that if the diapers, after wearing, were rinsed in a 1:4000 solution of mercuric chloride and allowed to dry, the production of ammonia ceased. In severe cases, he recommended the application of Lassar's paste with 4 per cent balsam of Peru; however, in the average case the treatment of the diapers was sufficient.

There are many kinds of insects which frequently bite human beings especially during the summer months. Those insects which are apt to be especially annoying are: (1) the common flea or *Pulex irritans*, (2) chicken louse (*Dermanyssus avium*), (3) mosquito (*Culex anxifer*), (4) gnat (*Culex pipiens*), (5) various types of flies of which the black fly of the genus *Simulium* causes the most intense local reaction, (6) bee, wasps and ants, (7) Harvest bug or *leptus*, (8) chigger (*Pulex penetrans*). There are other insects which may prove troublesome to man in various localities but this incomplete list includes the most common insects which are encountered in the temperate climate during the summer months.

The cutaneous manifestations of most of the various insect bites have one characteristic in common—namely the early lesion is urticarial. The intensity of the local reaction varies with the type of insect, but more particularly with the susceptibility of the individual who is bitten.

The lesions may be few or numerous; they occur most frequently on the exposed portions of the body and on the lower portions of the legs, about the ankles and on the feet. The most common type of lesion is a small erythematous spot or

an urticarial papule with a central puncta. If the inflammatory reaction is marked, a vesicle will develop at the site of the puncture. In some instances, the vesicle becomes a pustule: therefore, the eruption may assume the characteristics of an urticarial, papular, papulovesicular and papulopustular dermatitis. The bites of some insects, such as the flea and the black fly, cause small hemorrhagic or purpuric spots at the site of injury. The flea often bites several times in quick succession thereby producing a row of bites. In the case of the chigger, the very small, impregnated female parasite burrows into the skin and frequently produces small cutaneous abscesses, swellings and large vesicles or pustules. A secondary impetiginous dermatitis is not uncommon when chigger bites are numerous.

As a matter of general interest, we should add to the list of common insects first mentioned—the browntail moth. Strictly speaking the eruption sometimes produced by this moth is not an insect bite. This moth, so far as I am aware, does not have a wide distribution in the United States; however, if we are familiar with the dermatitis which results from contact with this moth or its caterpillar, we may find that it has spread from the New England states and adjacent portion of Canada where it has been responsible for large numbers of cases of dermatitis. If I have seen a case of browntail moth dermatitis, I have failed to recognize the condition. G. C. White of Boston was the first to recognize and report cases of browntail moth dermatitis, and later his colleagues, Meeks, Towle, and others added to our knowledge of this condition. In 1909 Potter<sup>7</sup> reviewed the literature and reported a case of generalized dermatitis which resulted from contact with this moth. Although it was known that the dermatitis resulted from the penetration into the skin of the barbed nettling hairs of the moth and its caterpillar, it remained for Tyzzer<sup>8</sup> to prove that the irritation in the case of browntail moth dermatitis was due to a poisonous substance contained within the hairs.

The caterpillar reaches its full growth in June and the

moth emerges about the middle of July; consequently, this condition is seen most frequently during these months. It may occur at other seasons following contact with clothing in which the barbed hairs have lodged and may result in a dermatitis. The eruption which is usually produced by the barbed nettling hairs of the browntail moth most frequently involves the face, neck and arms. It appears as itchy erythematous macules which develop into pea-sized urticarial lesions. In severe cases, the lesions may become confluent; however, the tendency is for them to remain discrete.

The treatment of most insect bites is directed toward relieving the itching because in most instances, the local inflammatory reaction which follows the sting will subside in a day or so. In the case of the chigger, the insect should be removed from the skin. Stelwagon and Gaskill<sup>9</sup> state that this may be accomplished by rubbing in fats or petrolatum. To relieve the itching, the calamine, phenol and menthol lotion previously mentioned is very satisfactory. In cases complicated by an impetiginous infection, the lesions should be cleansed well by removing all crusts and all the undermined epidermis of bullous lesions. The involved areas should then be treated with potassium permanganate solutions and the ammoniated mercury ointment suggested for the impetiginous infection which sometimes occurs in miliaria. Five per cent gentian violet in 20 per cent alcohol painted on the cleansed lesions is a dry type of treatment which may, at times, be substituted for the permanganate packs and mercury ointment.

#### DERMATITIS VENENATA

Dermatitis venenata in its broadest meaning refers to any dermatitis which develops in individuals after they have come in contact with various substances to which they are sensitive, usually chemicals or some type of plant. Eruptions resulting from contact with common irritants such as strong acids which are injurious to all individuals are to be distinguished from dermatitis venenata. For the present, we are not interested in the varied clinical manifestations of dermatitis venenata in

its broadest meaning. We will consider only the dermatitis caused by plants, particularly ivy dermatitis. Although the list of plants known to cause a dermatitis is constantly being increased, poison ivy or *Rhus toxicodendron* is the plant which is responsible for the largest number of cases. Ivy dermatitis is characterized as an acute erythematous, edematous, vesicular eruption. The vesicles vary in size from a pinhead to that of a split pea. In severe cases, there is considerable edema with formation of bullae. The development of vesicles along a scratch mark is a sign of diagnostic importance as it signifies that some injurious substance was deposited on the skin at the time the injury was sustained.

The areas of predilection for ivy dermatitis are the exposed surfaces of the body—the face, neck, hands and arms and in children about the knees. In many cases, the dermatitis eventually develops on other portions of the body as the irritant is spread by the hands and clothing. Males invariably develop a dermatitis on the genitalia because of contact with the hands during micturition.

A specific treatment for ivy poisoning has not been discovered. Many remedies have been proposed but none can be said to be particularly efficacious. The susceptibility of the individual, the extent of the contact as well as the care which has been exercised to prevent the dissemination of the irritant over the cutaneous surfaces not only influences the severity of the dermatitis, but also affects its duration and its apparent response to therapy. Treatment should be directed toward the removal or neutralization of the irritant, the prevention of its dissemination, and the relief of subjective symptoms. Another procedure which is of questionable value is the use of the *Rhus* antigen as a therapeutic and preventative measure.

McNair<sup>10</sup> has shown that the irritant of *Rhus toxicodendron* is a nonvolatile resinous sap, the active principle of which is lobinol. Lobinol is soluble in ether, chloroform and alcohol, and is precipitated by lead acetate. McNair also speaks favorably of the use of potassium permanganate which was advocated by Syme<sup>11</sup> for the treatment of ivy dermatitis.

The various types of treatment which have been advocated cannot be discussed; however, the following procedures will suffice in most instances. The involved areas are first mopped with cotton saturated with a solution of equal parts of alcohol and ether. One small sponge should be used once or twice and then discarded. The vesicles and bullae are drained using aseptic precautions and their contents removed from the surface of the skin. The skin is then mopped with a 0.5 to 1 per cent aqueous solution of potassium permanganate and allowed to dry. After this, calamine lotion with 1 per cent phenol is applied. The permanganate and calamine lotion should be applied twice a day until the acute inflammation has subsided while the alcohol and ether is used but once in each area. If the dermatitis is disseminated, potassium permanganate baths are indicated. A bland ointment such as ung. zinc oxide with 3 or 4 per cent ichthyol should be used after desquamation has started.

The use of ferric chloride is undesirable because of the danger of permanent discoloration of the skin which may occur when this chemical comes in contact with cutaneous abrasions.

No doubt procedures other than the ones just mentioned are equally good, but rather than to enlarge upon the question of topical remedies, let us consider briefly the value of the Rhus antigen as a therapeutic and preventive measure. Obviously, the ideal procedure would be one which would desensitize a susceptible individual to any particular irritant and also prove equally effective therapeutically in cases in which a dermatitis had already occurred. Schamberg<sup>12</sup> was the first to record in the American literature the results of such an attempt in the case of ivy poisoning. He advocated the oral administration of a dilute tincture of Rhus toxicodendron. Later Strickler made several reports on the value of subcutaneous and intramuscular injections of alcoholic extracts of the ivy plant. In 1923<sup>13</sup> he combined his findings with a tabulation of results of other physicians who had used this antigen in the treatment of ivy dermatitis. All these reports were very encouraging and led to an extensive use of Rhus

antigen as a therapeutic and preventive measure. The early alcoholic extracts caused considerable pain but the more recent preparations in oil vehicles are painless. The early enthusiasm for this procedure resulted from clinical impressions rather than an evaluation of facts reached after a critical immunologic study. In more recent years, the pendulum of enthusiasm has swung back and at present there is considerable doubt regarding the efficacy of this type of treatment.

Early in the development of ivy antigen for desensitization, Corson<sup>14</sup> pointed out that the procedure was not entirely safe. He reported a case of a severe generalized dermatitis which developed soon after three injections of the Rhus antigen in a patient who was known to be sensitive to ivy. The antigen was given as a prophylactic measure.

In 1929 Templeton<sup>15</sup> again warned of the possible untoward reactions which may result from the toxin treatment of dermatitis venenata. He observed cases in which large urticarial swellings developed at the site of the injection as well as a generalized urticaria. In his cases, extracts of poison oak were used.

Krause and Weidman<sup>16</sup> were the first to analyze critically the various phases of this problem. They attempted to produce ivy dermatitis in animals but failed; consequently, they reported their findings which were based on experiments carried out on humans. They observed, among other things, that the dermatitis was not spread by the serum in the vesicles of ivy dermatitis, and that injection of ivy extracts did not protect susceptible individuals against a dermatitis when the irritant was applied to their skin. They doubted whether the antigen was of any therapeutic value.

Spain and Cooke<sup>17</sup> believe that some immunity to the Rhus toxin can be obtained by a series of injections starting with small doses of large dilutions of the extract. They feel that there is a degree of clinical immunity, even though no change can be demonstrated by patch test with the active principle. Gowen<sup>18</sup> obtained favorable therapeutic and prophylactic results with two injections of almond oil extract of Rhus toxic-

codendron. Other observers have not obtained such a good response to the use of the antigen; consequently, it occurred to Maisel<sup>10</sup> that immunization could best be obtained by subjecting the skin of a susceptible individual to contacts with small increasing doses of the extract of poison ivy. This was tried in one case with excellent results. The method used by Maisel was a daily bath in a measured quantity of water to which had been added a measured amount of the tincture of *Rhus toxicodendron*. The initial bath consisted of 4 drops of the tincture to 10 gallons of water. The amount of tincture of *Rhus toxicodendron* was increased and the amount of water decreased until on the twenty-fifth day the bath consisted of 15 cc. of the tincture and 4 gallons of water. When 30 cc. of tincture to 4 gallons of water was used, an acute general pruritus would develop. Following this series of baths, the patch test with ivy extract was only slightly positive at the end of twenty-four hours.

Straus<sup>20</sup> was unable to produce sensitization in new-born infants either by the oral administration or by the subcutaneous injections of an alcoholic extract of poison ivy; yet in another series of experiments he was able to sensitize 72.9 per cent of 48 infants by the application of an ivy paste to the skin. These observations are both interesting and significant because they present the question that if the oral or subcutaneous injections of ivy extract cannot sensitize an individual, it is unlikely that a similar procedure will desensitize one who is susceptible to the plant. The fact that acquired sensitization to ivy is produced by contact of the epidermis with the resinous sap of the plant as well as the observation of Maisel tends to further justify this presumption.

My experience with the ivy antigen has been confined mainly to its use as a therapeutic agent. I have seen the patients after the acute dermatitis has already been established and they have failed to return later for prophylactic treatment. However, I have seen several cases in which injections of the *Rhus* antigen had failed to prevent ivy poisoning. I have observed instances of the complication mentioned by Temple-

ton<sup>15</sup> and have failed to see a single case in which I was convinced that the use of the antigen was of distinct value as a therapeutic measure.

I realize that the question of the advisability of using Rhus antigen is still a debatable one; however, I believe that the observations previously cited create considerable doubt regarding the efficacy of this procedure. In any event, the early enthusiasm of the profession for this use of ivy antigen has waned materially.

Another type of contact dermatitis which is being more frequently recognized is that produced by plants of the ragweed family. The dermatitis may result from contact with the plant or its pollen. The irritant is contained in both the oil of the plant and in the pollen. In susceptible individuals, contact with the pollen in the dust of the air is sufficient to produce a dermatitis. There is a seasonal occurrence of ragweed dermatitis. It appears late in July or early in August and disappears after the first frost. However, if the susceptible individual is a farmer, recurrences may occur at other times of the year as a result of contact with the weed or its pollen in hay and grain. Brunsting and Anderson<sup>21</sup> recently reviewed the literature and reported 18 cases of ragweed dermatitis and pointed out that since all the reported cases of ragweed dermatitis have occurred in adults, evidently sensitivity to this plant is acquired only after long contact with the irritant. The eruption consists of a diffuse redness with a variable amount of edema and a very slight amount of vesiculation as contrasted with the marked vesiculation of ivy dermatitis. The dermatitis is more of the subacute type. The exposed surfaces are the areas of predilection.

The treatment of ragweed dermatitis is symptomatically similar to that recommended for dermatitis venenata—namely, cooling, evaporating lotions or wet dressings in the acute stage and bland ointments as the inflammatory reaction subsides.

Brunsting and Anderson<sup>21</sup> treated 8 cases with intramuscular injections of the specific oils of the ragweed which had been



recommended by other observers. Their results were inconclusive.

At the time of their report they were giving preseasonal treatment to a few patients but have not reported on the value of this procedure.

### SUMMARY

We have briefly discussed a few of the dermatoses commonly seen during the summer months. We had hoped to discuss other dermatoses, such as impetigo and epidermophyton infection, which are seen frequently during this season of the year, but space will not permit. We should bear in mind that although the dermatoses which we have discussed are encountered most frequently during the warm weather they may also be seen during the winter months.

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## PRURITUS VULVAE

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ITCHING of the vulva is a common complaint which occurs most frequently at the menopause or during the middle decades of life. The discomfort may vary from that of a slight sensation to that of a very distressing and agonizing pruritus. Whether pruritus is generalized or localized, it is a subjective symptom and not a disease in itself.

The mechanism of the production of itching is obscure; however, its causes are many and the degree of the sensation is influenced by individual susceptibilities and the intensity of the particular stimulus or irritant. Clinical observation has demonstrated that in many instances pruritus vulvae must be considered as a symptom of some disturbance which is localized in the anogenital region or as a manifestation of some general or systemic disease, but in a large group of cases of pruritus vulvae definite causes cannot be determined. However, with a better understanding of the rôle of allergy, nutritional deficiencies, endocrine dysfunctions and psychoneurogenic factors, the frequency with which diagnoses of idiopathic pruritus are made will decrease.

Because of the multiple and varied factors which may produce this distressing condition, it is necessary that in each case a painstaking investigation be made for possible local, regional or constitutional abnormalities which may be of etiologic importance. In some instances, the cause of pruritus vulvae can easily be determined and eradicated, but in a large number of cases in which the condition is chronic, a very careful study is necessary. Although in many instances the reward for such a laborious and time-consuming task will be

disappointing, it should be recommended in all cases where the etiology is obscure; otherwise, we would be guilty of dereliction of duty by simply advising the patient to use some palliative treatment which frequently gives only temporary relief.

All the conditions which have been reported as causes of pruritus vulvae have not been included in this discussion but only the more common causes will be considered. A grouping similar to that used by Davidson<sup>1</sup> is satisfactory:

I. Pruritus vulvae resulting from an inflammatory process in the skin and mucous membranes of the vulva and genito-urinary tract. In cases in which there is an associated pruritus ani, pathologic changes in the rectum and about the anus must be looked for. In this group, the most common, direct and contributing factors are:

(a) Bacterial infection—*Bacillus coli*, staphylococci or streptococci.

(b) Fungous infection.

(c) Parasitic infestations.

1. *Trichomonas vaginalis*.

2. *Oxyuris vermicularis* or pinworm.

(d) Fixed drug eruption, such as phenolphthalein.

(e) Hypersensitivity to chemicals commonly used in douches or as contraceptives.

(f) Cervicitis, cystitis and proctitis.

II. Cases where itching is a symptom of some particular dermatosis in which lesions are either limited to the anogenital region or are associated with characteristic lesions on other portions of the body such as:

(a) Lichen planus.

(b) Kraurosis, or leukoplakia vulvae.

(c) Circumscribed neurodermatitis.

III. Cases in which the pruritus is a symptom of some systemic or visceral disease. The most common of these diseases are:

(a) Diabetes.

(b) Deficiency states such as achlorhydric anemia.

- (c) Food allergy.
- (d) Endocrine dysfunction.
- (e) Psychoneurosis.
- (f) Chronic diseases of the abdominal and pelvic viscera.

IV. Cases of primary pruritus in which the itching is some unexplained irritation of the nerve terminals.

In pruritus vulvae, the itching is usually paroxysmal and is more severe at night. It may be limited to the region around the clitoris or the labia or the entire vulva may be involved; occasionally, there is an associated pruritus ani. The objective findings vary greatly. In severe chronic cases, the skin of the vulva is dry, slightly scaly and leathery, showing accentuated markings on the skin surface or cross hatching, which is characteristic of lichenification. There may be excoriations, and the skin surface around the clitoris and on the small labia is frequently gray, thickened and slightly edematous. These changes are the result of trauma resulting from scratching. Maceration of the epidermis with weeping and crusting may result from secondary infection. In some cases the objective findings are negligible; however, if the itching is severe and persistent, the scratching, which is inevitable, frequently produces lichenification of the skin. Occasionally when the complaint is of long standing the itching may be present for some time after the apparent cause has been removed.

What are some of the objective findings in the various groups of pruritus vulvae which have been mentioned?

I. (a) The importance of localized bacterial infection in the production of pruritus vulvae has not been determined. A few years ago the attention of the profession was aroused by the enthusiastic reports of Murray,<sup>2</sup> Winfield,<sup>3</sup> and Knowles and Carson<sup>4</sup> in the use of *Streptococcus faecalis* and *Bacillus coli* vaccines in the treatment of pruritus ani. In some of these cases, itching of the vulva also was present. The results reported following the use of this type of vaccine therapy were exceptionally encouraging, but these authors did not conduct their bacteriological studies carefully and they failed to

present convincing evidence that these organisms, which are practically always present in the anogenital region, were the specific cause of the pruritus. Later Montague<sup>6</sup> made a more careful study of this problem and although he favored the theory of bacterial infection in some cases, his observations indicated that the staphylococcus and colon bacillus were probably the infective agents. As Montague has aptly stated, the explanation of bacterial invasion as the cause of pruritus in the anogenital region is most alluring. However, there are no objective signs which may be considered as diagnostic evidence of a bacterial type of pruritus ani and vulvae.

(b) Fungous infections have a predisposition for the folds of the body where there is heat and moisture. The favorite sites for an epidermophyton infection are the feet, groins, gluteal folds and axillae. Consequently, it is not surprising that occasionally the folds of the vulva likewise become the site of this infection. In the cases of pruritus vulvae due to fungous infection, there is usually evidence of a similar infection in the groins or interdigital spaces of the feet. In all cases, the feet should be examined carefully for fissuring and maceration between the toes, vesiculation and desquamation on the plantar surfaces, and for well demarcated orbicular, brick-red, slightly scaly plaques in the groins and about the anus. The absence of lesions in these regions does not rule out the possibility of a fungal infection of the vulva. The labia and skin of the vulva should be examined carefully for erythematous raised plaques which may be small and only fairly well demarcated. If such lesions are present, repeated scrapings and cultures should be made before the possibility of a fungous infection can be ruled out. In some instances, there may be only a few small areas, while in others there are lesions in the groin, gluteal folds, and on the vulva and in cases of long standing, the skin of the vulva becomes lichenified. Ultimately, a positive diagnosis depends upon the demonstration of a pathogenic fungus from the lesion. Yeast organisms are frequently found in suspected lesions; however, Castellani<sup>6</sup> doubts if they are of etiologic importance. The

number of cases in which an epidermophyton infection is limited to the vulva is small as compared with the incidence of this infection. Nevertheless, it is an important cause of pruritus vulvae and must be considered in differential diagnosis of this condition.

(c) *Trichomonas vaginalis* is a protozoan parasite which may produce a vaginitis with resulting pruritus vulvae. In this type of vaginitis the mucous membrane of the vagina and vaginal orifice are bright red, granular in appearance and covered with a profuse, frothy, thin, yellowish foul discharge. Before a definite diagnosis may be made, the parasite must be demonstrated in the vaginal exudate. This is accomplished by microscopic examination of material obtained from the deep portion of the vagina by means of vaginal speculum and small cotton applicators. The applicators which are covered with the exudate are immediately placed in a small amount of warm normal saline solution. A hanging drop preparation of this mixture of the saline and exudate should be examined while the solution is warm, because chilling stops the motility of the organisms. The organisms are recognized as motile, flagellated ameboid cells.

The degree of vaginitis produced by the infestation of the trichomonas is variable. In some patients, the vaginal discharge contains the trichomonads, but there are only slight or no subjective symptoms. In certain individuals, the rectum and bladder may be infected with the parasite, thus becoming foci for vaginal reinfection. Sayer<sup>7</sup> emphasizes the importance of eradicating these residual habitats of the trichomonas. In vulvovaginitis trichomonalis, the patient complains of a burning and itching at the vaginal orifice and within the vagina and this may be severe. The copious discharge may produce a secondary dermatitis of the vulva which is more acute than that seen in chronic cases of pruritus vulvae with resultant lichenification.

An infestation by *Oxyuris vermicularis* or pinworm may be responsible for pruritus vulvae and this is especially true in children because they are affected by this intestinal parasite



more frequently than are adults. The female worms work their way out of the anus, usually at night, and may enter the vagina. In cases of pruritus ani associated with pruritus vulvae in which there are nocturnal exacerbations, particularly in children, *Oxyuris vermicularis* should be excluded as an etiologic factor. When this parasite is present, the skin between the buttocks and on the perineum is usually excoriated and a diagnosis is established by demonstrating the presence of the parasite. The gravid female worm moves from the small intestine to the rectum, where it deposits its ova, and scratching of the anus spreads the ova over the skin around the anus. Consequently, scrapings from this region will often contain the ova of the pinworm in infested individuals. The stool should also be examined for ova and for female worms.

(d) It has been definitely established that phenolphthalein, antipyrine, amidopyrine and arsphenamine may produce a fixed, localized eruption. The involved areas show periodic efflorescences and remissions of an acute, erythematous, edematous dermatitis and resultant pigmentary changes. Involvement of the male genitalia has been observed, although such cases are rare. The possibility of a fixed drug eruption—especially phenolphthalein which is limited to the vulva must be kept in mind. I have observed one case of periodic pruritus vulvae in which there was some edema and a brownish purple pigmentation of the small labia and skin in the region of the clitoris. These symptoms almost completely disappeared following cessation of the use of a cathartic containing phenolphthalein.

(e) Certain chemical ingredients of douche powders, contraceptive jellies, and vaginal suppositories will produce a vaginitis and dermatitis venenata on the vulva in susceptible individuals. Obermayer,<sup>8</sup> Vaughan and Fowlkes,<sup>9</sup> and Rattner<sup>10</sup> have reported cases of dermatitis on the male genitalia which resulted from sensitization to the rubber of condoms. I am unaware of any recorded case of vulvitis resulting from contact with condoms; however, I feel that the possibility of this factor as a cause of pruritus vulvae should be kept in

mind. Vaginitis and dermatitis of the vulva resulting from contact with chemicals to which the patient is sensitive does not differ fundamentally from contact dermatitis elsewhere on the body. Usually, there is an acute onset at a variable time after contact with the offending agent, and edema, erythema and vesiculation depend upon the degree of inflammatory reaction which is produced. In this group of cases, an accurate history and the patch tests for suspected preparations and their various ingredients are procedures of prime importance.

(f) The exudate arising from a catarrhal cervicitis and endometritis or the irritation of urine in the presence of cystitis may precipitate pruritus of the vulva. At the onset, there may be very little visible change in the vulva; however, if these sources of irritative agents are not eradicated, continued scratching may produce the thickened, leathery skin frequently observed in these cases. If there is an associated pruritus ani, a proctoscopic examination is indicated. If a proctitis is present, appropriate treatment should be instituted. It is very difficult to evaluate the etiologic importance of cervicitis, endometritis, cystitis, and proctitis in pruritus of the anogenital region because the incidence of these conditions unassociated with pruritus is much greater than the incidence when pruritus ani and vulvae are present. Nevertheless, the discharges from these infected areas may be irritative to the inflamed surfaces of the vulva and consequently, if these conditions are present, their treatment should be included in the management of pruritus vulvae.

II. The lesions of certain pruritus dermatoses may be limited to or may involve the vulva as a part of a more disseminated eruption. The dermatoses which should be given special consideration are lichen planus,<sup>11</sup> kraurosis vulvae, leukoplakic vulvitis, and circumscribed neurodermatitis.

(a) The characteristic lesion of lichen planus is a flat, angular, shiny, violaceous, pruritic papule. Larger, raised, violaceous, scaly plaques or umbilicated papules may be present. These larger lesions will contain a reticulation of gray streaks and punctae which is pathognomonic of this disease and

which is characteristic of lichen planus which involves the mucous membranes of the mouth or genitalia. The eruption of lichen planus may be fairly well localized to the flexoral surfaces of the arms, dorsum of the hands, and to the lower extremities or it may be disseminated, and in each instance the mucosa may or may not be involved. Likewise, in a small number of cases, lichen planus may be limited to the mucous membrane of the mouth or to the mucocutaneous surfaces of the female genitalia. In cases of pruritus vulvae in which such lesions occur on the vulva or involve the vaginal introitus, the whole cutaneous surface should be examined carefully for lesions of lichen planus. A rare type of lichen planus which sometimes involves the vulva is that characterized by white, angular, flat, sclerotic and atrophic papules. The surfaces of the lesions are smooth, shiny and, at times, present small, black, horny comedo-like plugs. Usually associated cutaneous lesions of the same type are found which help to clarify the diagnosis. This condition is spoken of as lichen planus sclerosus et atrophicus. This variety of lichen planus so closely resembles the late stages of kraurosis vulvae that Montgomery and Culver<sup>12</sup> and F. Parkes Weber<sup>13</sup> have ventured the opinion that kraurosis vulvae is frequently a manifestation of lichen planus. Ketron and Ellis<sup>14</sup> have recently added white spot scleroderma to the list of conditions which may involve the vulva which thereby produces a clinical picture simulating kraurosis vulvae or leukoplakic vulvitis. They believe that some cases which are diagnosed as leukoplakia of the vulva are examples of white spot scleroderma.

(b) Kraurosis vulvae usually occurs at the time of or following the menopause and is rarely seen in young women. It is characterized by atrophy, sclerosis or scarring, and intense pruritus. Since leukoplakia and carcinomatous degeneration are sometimes late developments in kraurosis, some authors have used leukoplakic vulvitis and kraurosis as synonymous terms. Taussig,<sup>15</sup> Wise,<sup>16</sup> Montgomery<sup>17</sup> and others, however, distinguish between true kraurosis vulvae and leukoplakic vulvitis. Taussig feels that in the former

there is an atrophy of the labia minora, vestibule and tissues in the region of the urethra and clitoris. At first, the skin is red and glistening but later it becomes pale and smooth. The vaginal orifice becomes narrowed, coitus becomes painful or impossible, and itching is not necessarily a troublesome symptom. On the other hand, itching is intense in leukoplakic vulvitis, leukoplakia is a marked feature and carcinomatous development is common. A recent article by Adair and Davis<sup>18</sup> gives an excellent description of this condition and they use the broader descriptive term, chronic atrophic dermatitis of the vulva rather than the terms kraurosis and leukoplakia vulvitis. Kraurosis vulvae should not be confused with the physiological atrophy which occurs at this time or following castration in which itching may occur, but is not so intense or severe as that of kraurosis.

Adair and Davis<sup>18</sup> describe three stages of this disease: (1) an initial stage of itching associated with edema limited to the labia and preputial folds; in this stage there are no signs which are diagnostic of kraurosis. (2) An intermediate stage in which the skin becomes white, shiny, mottled, and early atrophic changes appear. In this stage the condition extends to the perineum. (3) A late stage in which there is marked atrophy, sclerosis, fissuring and leukoplakia.

(c) Circumscribed neurodermatitis is characterized by the occurrence of localized areas of lichenification. The itching accompanying this condition is primary and appears before any change can be detected in the skin; the pruritus is intense and paroxysmal in type. The visible changes in the skin appear later as a result of the trauma of scratching. The lesions may be irregular in outline, but frequently they are oval and vary in size from that of the palm to that of a half dollar. One or more lesions may be present which have a predilection for the nape and lateral surfaces of the neck, the extensor surfaces of the forearms, inner surfaces of the thighs and about the ankles. The central portion of the plaque is thickened and, due to accentuation of the normal lines of the skin, its surface is divided into small irregular areas on which there

may be small, dry, adherent scales. The periphery of the patch is thinner and poorly demarcated. There is no tendency to symmetrical distribution of the lesions.

The cause of circumscribed neurodermatitis is unknown. It is a common condition which occurs more frequently in women than in men, and it is found usually in the emotional, highstrung type of person. Worry, overwork, and other factors which adversely affect an unstable nervous system are important factors in the causation or exacerbation of a neurodermatitis.

This disease occasionally involves the vulva in the form of an isolated plaque on one of the large labia, or it may involve the hairy surfaces above the clitoris and extend downward to involve the labia majora. When this type of lesion is present, the areas of predilection mentioned above should be examined for plaques of primary lichenification because such associated lesions help in the interpretation of the vulvar lesion.

III. (a) The most important systemic disease of which pruritus vulvae may be a symptom is diabetes mellitus, and the possibility of diabetes must be considered in all cases of pruritus vulvae. In fact, this may be the initial complaint which causes the diabetic to seek medical advice. When a slightly elevated fasting blood sugar level is found, a glucose tolerance test should be done. Itching of the vulva may occur when the hyperglycemia is not accompanied by glycosuria, as in the case observed by McPherson<sup>14</sup>; however, glycosuria usually is present. In diabetic vulvitis, there is maceration of the epidermis, with erosions, weeping and an accumulation of debris in the folds of the vulva. The urethral orifice is edematous and the patient complains of dysuria. A secondary infection occurs and in severe cases, an intertriginous and at times an impetiginous dermatitis develops in the groins and on the inner surfaces of the thighs.

(b) It is possible that systemic disturbances resulting from nutritional deficiency in rare instances may be of etiologic importance in pruritus vulvae. The anogenital region is com-

monly involved in pellagra, a syndrome which unquestionably is a deficiency disease. The possibility that pruritus vulvae may, in some instances, be a manifestation of a deficiency state is suggested by the observation of Swift,<sup>20</sup> who recently reported 4 cases of pruritus vulvae in individuals with achlor-hydric anemia. In these cases, the itching disappeared following the administration of iron and hydrochloric acid. Previously, such pruritus had been considered to be of neurotic origin.

(c) It is doubtful whether food allergy is ever responsible for pruritus which is limited to the vulva. In recent years, the laity as well as the medical profession, has become so allergy conscious that both tend to overestimate the importance of food sensitization as etiologic factors in certain pruriginous dermatoses. Occasionally, we see an individual with the familiar eczema-asthma-hay fever complex who is troubled with chronic pruritus vulvae. In most of these cases, we obtain positive reaction to various foods when tested by the intradermal method; however, only a small percentage of these patients are noticeably benefited by a dietary regimen alone. This problem is a complicated one and the food allergy must be considered only as a component part. These patients frequently have signs of neurocirculatory instability, they are the victims of hereditary instabilities and constitutional inadequacies, and they are subjected to many environmental stimuli which tend to accentuate the psychoneurogenic factors which Stokes,<sup>21</sup> Becker<sup>22</sup> and Van de Erve and Becker<sup>23</sup> have so ably discussed. The management of this type of case must of necessity include a proper evaluation of all its phases and not be limited to a nonallergic regimen.

(d) Since pruritus vulvae occurs frequently near the time of the menopause, and since at times it is worse a few days preceding menstruation, some endocrine dysfunction has been suggested as an etiologic factor. At the menopause, there is a decrease in ovarian function and consequently, some observers have used follicular ovarian hormones in the treatment of this condition and have reported good results in a few cases.

The estrogenic hormone which has been used is that extracted from the urine of pregnant women and the commercial products which are available in this country are theelin, progynon and folliculin-menformon. It seems logical to suspect that endocrine dysfunction in some cases may contribute to the causation of pruritus vulvae, yet such an assumption for the present is largely speculative. It is possible that in the future, the endocrinologists will make discoveries which will be helpful in solving some of these recalcitrant problems.

(e) There is another group of patients in whom pruritus vulvae is the result of a psychoneurosis resulting from repressed sexual desires, marital incompatibility, masturbation, and practices resulting in ungratified sex life. Hazen and Whitmore<sup>24</sup> and Stokes<sup>25</sup> have emphasized the importance of sexual psychoses in pruritus vulvae as well as in some other types of pruriginous dermatoses.

(f) The etiologic importance of certain chronic diseases of the abdominal and pelvic viscera in pruritus vulvae, has not been established definitely. Cases in which pruritus of the anogenital region has been relieved following the removal of a chronically infected appendix have been reported. However, such cases are seen very infrequently and the incidence of pruritus which is limited to this region and which is associated with chronic disease of the viscera, is low.

Montague<sup>20</sup> has expressed an opinion that some cases of pruritus ani may result from congestion, inflammation, hyperplasia or any change in volume of a viscus which disturbs the nerves of its capsule. He assumes that afferent stimuli which arise in the capsule of the viscus are sent to the central nervous system, thereby stimulating the somatic afferent nerves by creating an irritative focus in the posterior ganglia. This irritation is then referred to the skin area supplied by the particular somatic nerve. He thinks that this is analogous in principle to misreference of pain and feels that the itching of the perineum in diabetes is primarily due to afferent stimuli arising from a change in volume of the liver or of a chronic pancreatitis. This theory is open to question; however, these

observations demonstrate the advisability of looking for evidence of chronic diseases of the abdominal and pelvic viscera in cases of persistent pruritus vulvae in which the etiology is obscure. Montague's remarks are limited to the discussion of pruritus ani, but the same theory is equally applicable to pruritus vulvae.

The most common conditions in which pruritus vulvae may occur have been enumerated. No doubt other less obvious factors are operative. A number of obstinate cases still remain in which no satisfactory cause can be found, but for the present, we must consider these as examples of primary or idiopathic pruritus.

#### TREATMENT

The rationale and success of the treatment which is recommended for any ailment is dependent upon a proper evaluation of the general condition of the patient and the possibility of removal of any specific or underlying etiologic factors which are discovered. Although we are unable to find a specific cause in many cases of pruritus vulvae, a thorough investigation of each case should be made before we are justified in limiting our treatment to measures directed toward symptomatic relief.

If systemic disturbances such as anemia, gout, diabetes, hypothyroidism or other types of endocrine dysfunction are present, they must receive appropriate treatment. The possibility of successful results will be greatly enhanced if the physician is capable of eliciting and correcting the psychoneurogenic factors which frequently play an important part in the causation of generalized and localized pruritus. It is important to look for signs of neurocirculatory instability, to consider the personality of the patient and her reaction to social and financial burdens.

An accurate history of the patient's sexual life is important. This phase of the problem should be discussed only after the confidence and cooperation of the patient is assured. Some difficulty may be encountered in the case of an unmarried woman; but this approach should not be neglected in cases of chronic, persistent pruritus vulvae. The manage-



ment of cases due to a psychoneurosis resulting from repressed sexual desires, marital incompatibility, masturbation, etc., must be individualized to fit each particular case.

Local treatment to the anogenital region will necessarily vary, depending upon the type of local disturbance which is present. The type of local infection and the degree of the inflammatory reaction should determine the type of treatment best suited in each case. Since intense pruritus may be relieved by topical applications which are sufficiently stimulating to substitute the sensation of pain for that of itching, we frequently see patients who are suffering from the effects of too irritative applications. Such instances of overtreatment are usually the result of self-medication or injudicious remedies advised by the physician.

Cleanliness is the first essential to proper management of pruritus of the anogenital region. Consequently, treatment of an existing cervicitis, proctitis, or cystitis must not be neglected. Cleansing douches are important and the folds of the vulva should be washed gently at least once a day. In case of acute vulvovaginitis resulting from chemicals used in the douche, the cleansing should be accomplished with soothing measures such as warm saline or boric acid solution.

Many formulae may be used for the relief of itching and each physician has his favorite remedies; consequently, in general, moist packs or soothing evaporating lotions should be used in cases of acute, edematous, vesicular or weeping vulvitis while stimulating, parasitocidal, and antipruritic ointments are indicated in the various types of chronic vulvitis. In acute cases, moist compresses of warm potassium permanganate solution (1: 10,000); Burrow's solution (1 part to 12 or 15 parts of water); warm hypertonic saline solution, or a saturated solution of boric acid alternating with applications of calamine lotion or calamine liniment with 1 or 2 per cent of phenol and  $\frac{1}{4}$  per cent menthol will prove beneficial. In subacute conditions, an ointment of 2 to 5 per cent ichthyol and 1 per cent of phenol in unguentum zinc oxide may be advised.

A fungous infection usually produces a chronic or sub-acute vulvitis in which the use of stronger, keratolytic, and parasiticial agents are indicated. If the feet, groins, or the gluteal folds are involved, these areas should be treated also. There is no specific remedy for this common infection. The organism is usually confined to the epidermis, and keratolytic and parasiticial agents are indicated. Unfortunately, the tissues will not tolerate parasiticial agents in concentration sufficient to kill the fungi and therefore, the efficacy of modern treatment depends mainly upon the removal of the organism by the use of keratolytic drugs. Two of the most useful keratolytic agents are salicylic acid and benzoic acid. These drugs are most frequently used in the form of the popular Whitfield's ointment, which is a very satisfactory preparation. Full-strength Whitfield's ointment should not be applied to the vulva and the following one-half strength has been found to be most beneficial:

R	Gm. vel cc.
Salicylic acid. . . . .	9
Benzoic acid. . . . .	1. 8
Soft paraffin. . . . .	8
Coconut oil. . . . .	.q. s. ad 30
M. and fr. ung.	

Two or 5 per cent ammoniated mercury may be added to this ointment.

Some patients prefer a dry and cleaner type of treatment consisting of applying moist potassium permanganate packs (1:5000) for an hour twice a day, followed by an alcoholic solution of salicylic acid and benzoic acid such as:

R	Gm. vel cc.
Tr. cudbear. . . . .	1 5
Salicylic acid . . . . .	3 6
Benzoic acid . . . . .	4 8
Alcohol, 70 per cent . . . . .	.q. s. ad 120

After the lotion has been applied, the surfaces should be covered with the following powder:

R	Gm. vel cc.
Thymol.....	5
Salicylic acid.....	3
Boric acid powder.....	80
Talcum.....	q. s. ad 120

This type of treatment has proved to be satisfactory in many cases in which the infection involves the inguinal region. Castellani<sup>6</sup> recommends Deek's ointment, which is:

R	Gm. vel cc.
Salicylic acid.....	4
Bismuth subnitrate.....	10
Mercury salicylate.....	4
Oil eucalyptus.....	4
Lanolin.....	30
Vas. alb.....	q. s. ad 100

Other parasiticial remedies may be used such as an ointment of 6 per cent sulphur and 4 per cent salicylic acid, or applications of 10 per cent silver nitrate; but regardless of the choice of remedy, the patient should be observed frequently or he should be instructed carefully in order to prevent a chemical dermatitis which results from prolonged use of these drugs. After the superficial epidermis has been removed, a bland ointment or lotion is indicated. Since recurrences are frequent the treatment may have to be repeated several times. Infected toenails should be removed and the patient must not neglect other foci such as the interdigital spaces on the feet. The intracutaneous injection of extracts of fungi such as trichophytin in an attempt to desensitize the individual to the organism has not been beneficial in a large percentage of cases.

The treatment of pruritus of vulvovaginitis trichomonalis is directed toward the eradication of the parasitic infestation. Gellhorn<sup>27</sup> recommends a dry type of treatment, using a powder of 12.5 per cent acetarsone in equal parts of kaolin and sodium bicarbonate. Sayer<sup>7</sup> advises scrubbing the vagina with an alkaline solution followed by a tampon saturated with 25 per cent neosilvol and emphasizes the necessity of treating the

residual foci in the bladder and rectum. Members of our staff have found carbarsone suppositories quite effective in cases of trichomonas infection. The patient is instructed to insert one suppository each night for a month. Douches are limited to one a week and the suppositories are to be used during the menstrual period. It is impossible to give a more detailed discussion of the treatment of this condition at this time. However, it is of interest to note that Davis<sup>28</sup> has found that in cases of senile vaginitis, with an associated trichomonas infestation, the organisms disappeared following the administration of an estrogenic hormone. He, therefore, suggests that a follicular hormone be used in cases of *Trichomonas vaginalis* occurring in the postmenopausal period.

In cases in which an infestation of *Oxyuris vermicularis* is present, injections of a decoction of quassia will remove the worms from the rectum. The worms must also be removed from the small intestine by the usual procedure of a light diet and the administration of castor oil followed by santonin.

Since the etiology of lichen planus and circumscribed neurodermatitis is obscure, our treatment of these conditions is empirical. Lichen planus will frequently respond to intramuscular injections of mercury or bismuth; however, lichen planus of the mucous membranes is often very resistant to treatment. One cc. of 1 per cent bichloride of mercury twice a week or 2 grains of bismuth salicylate once a week is often efficacious in the treatment of lichen planus. The oral administration of arsenic in the form of Fowler's solution or preferably asiatic pills ( $\frac{1}{10}$  grain arsenic and 1 grain black pepper) is at times beneficial in neurodermatitis. Topical applications of antipruritic and stimulating ointments should be advised. The following prescriptions are useful:

R	Gm. vel cc.
Phenol . . . . .	3
Menthol . . . . .	1
Camphor . . . . .	3
Unsat. zinc oxide . . . . .	q. s. ad 30

R	Gm. vel cc.
Liq. carbonis deterg.....	1   5
Ammon. mercury.....	1
Ung. boric acid.....	q. s. ad 30

R	Gm. vel cc.
Ung. picis. liq.....	4
Zinc oxide.....	4
Starch powder.....	8
Diachylon oint.....	4
Vas. alb.....	q. s. ad 30

Roentgen therapy is especially useful in the treatment of lichen planus and circumscribed neurodermatitis. Careful consideration should be given to possible psychogenic factors in cases of neurodermatitis and sedatives such as bromides or phenobarbital are especially helpful, but should not be given over long periods.

Kraurosis and leukoplakic vulvitis do not respond to palliative measures. These conditions should be treated surgically either by section of the cutaneous nerves or by vulvectomy in cases with extensive leukoplakia.

With the rapid advances that are being made in endocrinology, it is probable that hormone therapy will prove beneficial in selected cases of pruritus vulvae. A follicular hormone should be tried in cases occurring at or after the menopause or when there is reason to believe that there is a deficiency of the estrogenic substance. Davis<sup>28</sup> obtained good results by the use of a follicular hormone in pruritus vulvae which occurred in association with senile vaginitis.

Roentgen therapy is the most valuable single aid in the treatment of pruritus vulvae, but it should be emphasized that the roentgen ray is only an adjunct to the therapy of pruritus vulvae and does not obviate the necessity of a thorough investigation of each case. In most instances, the patient experiences complete relief after three or four treatments, but in rare instances, the itching is aggravated by roentgen therapy. This type of therapy must be used cautiously to avoid radio-dermatitis. The administration of a fractional dose of one

fourth of a skin unit at weekly intervals as devised by McKee<sup>29</sup> is the technic of choice. This will give relief in many instances for weeks at a time. Recurrences of the pruritus following roentgen therapy are frequent, consequently the patient will return or consult another physician with a request for more treatment. Because of this, the dosage and technic of previous treatments should be determined before further roentgen therapy is administered. One fourth of a skin unit may safely be administered once a week for eight to ten weeks. Irritative applications should not be used in conjunction with roentgen therapy.

Vaccine therapy is of little value. It is probable that the good results obtained by Murray<sup>2</sup> and others with this type of treatment were due to a foreign protein reaction rather than to a specific effect of the vaccine. These results could probably be obtained by the use of any other foreign proteins commonly used in the form of milk preparations, one of the most common being that of aolan.

#### SUMMARY

Many phases of this subject have necessarily been omitted. The more common conditions which may produce pruritus vulvae have been discussed and a few therapeutic suggestions which we have found helpful have been given. The physician should consider pruritus vulvae as a symptom rather than a disease and should examine each patient thoroughly for systemic and local disturbances which may contribute toward the causation of this distressing symptom. This is an extremely complex problem and the results of our efforts are often disappointing; nevertheless a fair percentage of patients can be relieved if they are adequately studied.

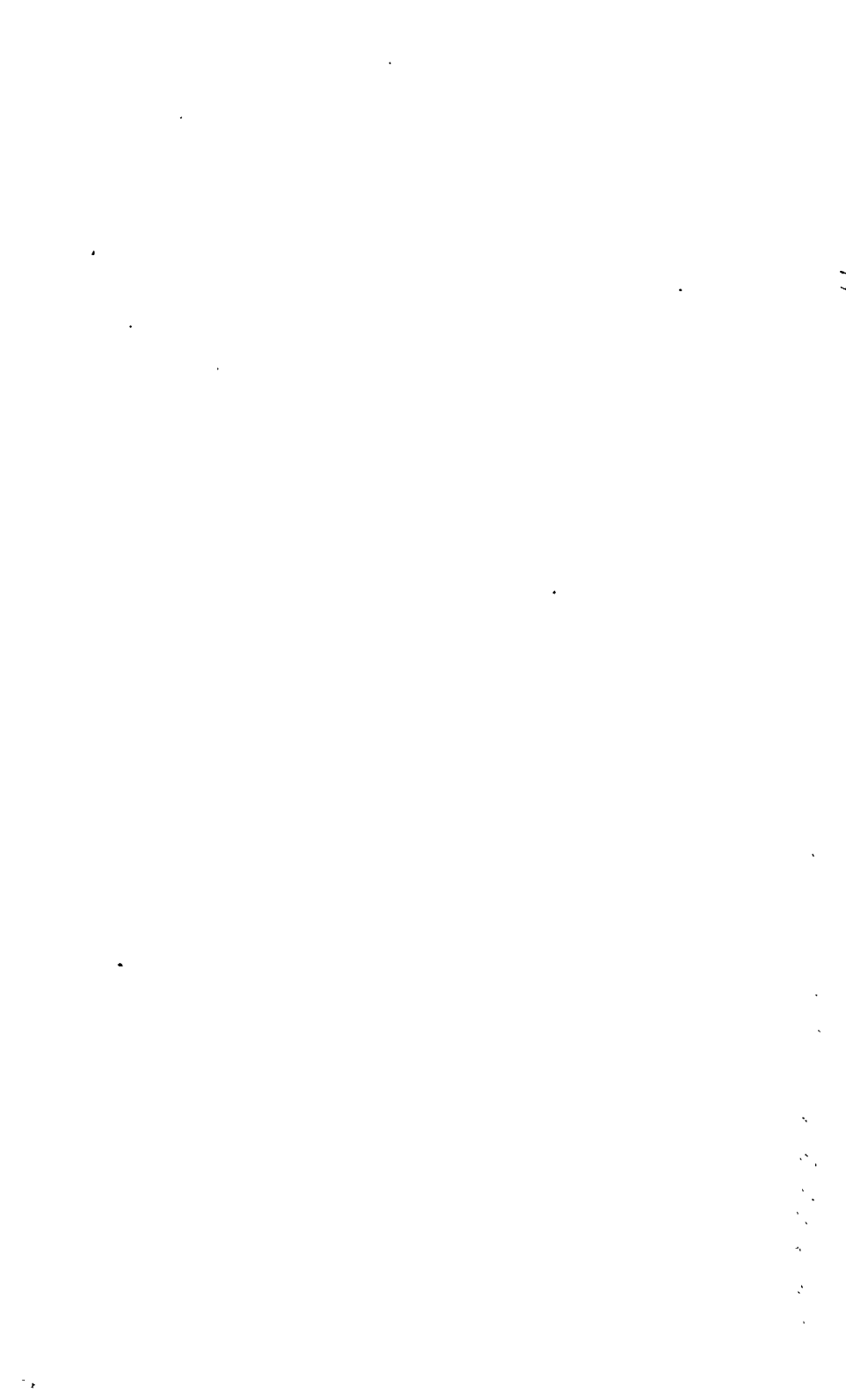
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## THE TREATMENT OF HAY FEVER IN GENERAL PRACTICE

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It has been estimated that from 2 to 3.5 per cent of all people suffer during some period of their lives with pollen allergy. One may casually assume that this figure is not impressive, but considering that in a city with a population of 1,000,000 there are 20,000 people who have or who have had pollen allergy, more than a casual interest must be given to the large problem of giving satisfactory relief to these sufferers.

An increasing number of people with pollen allergy are rapidly becoming conscious of the recent strides in the allergic management of their problems. Likewise, many physicians each year are realizing the futility of attempting to give their patients satisfactory relief by limitation of their armamentarium to the various hay fever remedies, such as nose drops, coryza tablets, inhalations, ionization treatments and numerous other local surgical measures. Both patients and physicians are acknowledging the consistently satisfactory results which have been secured by thorough investigation for allergy followed by management based upon such studies. It is recognized by layman and physician alike that it is impracticable for the average hay fever sufferer to take extended and expensive trips into pollen-free areas. What then, is the proposed management of pollen allergy?

It is the consensus of opinion that the ultimate results in the treatment of patients with hay fever and asthma are dependent upon a satisfactory arrangement between the family physician and the patient. Therefore, the plan usually followed is to give complete and thorough allergy tests where

equipment and facilities are adequate and then have the patient return to his family physician for supervision of the course of treatment. If this plan were not followed, the majority of patients with pollen allergy could not entertain any thought of treatment except with the usual local nonspecific measures.

The purpose of this discussion is to present briefly the method of investigation and the plan of treatment observed in 400 patients with hay fever who were seen in the Department of Allergy during the past three years. The majority of these patients have not been under our personal care, but entered the clinic for diagnostic survey and advice as to therapy and then returned to their respective physicians for supervision of the prescribed method of treatment.

Most workers in allergy agree that the following requisites are necessary for pollen to produce hay fever and asthma:

1. The pollen must contain an excitant of hay fever.
2. The pollen must be wind-borne, as regards its mode of pollination.
3. The pollen must be produced in sufficiently large quantities.
4. The pollen must be sufficiently buoyant to be carried considerable distances.
5. The plant producing the pollen must be widely and abundantly distributed.

In Ohio and the surrounding section, there are three distinct hay fever seasons, the tree, grass and weed seasons. The tree season begins about the last week in April, reaches its height the last two weeks in May and continues through June. This produces a definite overlapping effect with the grass hay fever season. The trees fulfilling the requirements for production of hay fever are ash, black walnut, hickory, oak, poplar, elm, sycamore, birch, maple, beech, and willow.

The grass hay fever season begins about the third week in May, reaches its height the third week in June, and tapers off gradually to a nonactive stage about the second week in July. The season of 1935 was definitely prolonged due to climatic conditions, pollen being present in the atmosphere in sufficient

quantity to produce hay fever until the first week in August. Many patients, therefore, gave a history of failure to note a rest period between the grass and ragweed hay fever seasons. The grasses producing hay fever in Ohio and surrounding section are orchard grass, June grass, red top and timothy, and it is generally conceded that the latter is most abundant and produces more trouble. It is routine with many workers to use a large percentage of timothy pollen antigen and a smaller percentage of the antigen prepared from the other three hay-fever-producing pollens. Grasses other than those mentioned are, in our experience, of little clinical significance in this section of the country.

The fall hay fever season begins approximately August 10 or 15, according to weather conditions. Giant and short ragweed produce at least 95 per cent of the pollen appearing in the atmosphere during August, September and October. In Ohio and the surrounding sector, we see pollen-producing weeds which are active excitants of hay fever, but the scarcity of such weeds prevents them from being a factor in the production of clinical hay fever. In making daily pollen counts over a period of three years at the Cleveland Clinic, we have not been able to recognize and identify any type of weed pollen other than ragweed. Clinical study likewise emphasizes the fact that immunization to ragweed antigen produces excellent clinical relief if other allergy is controlled. We routinely include in our studies, pollen tests for goldenrod, English plantain, *Chenopodium*, marsh elder, Sorrel family, Russian thistle, cocklebur, corn, wheat, rye and we often note reactions, but no direct relationship to the patient's problem can be established.

During the past three years, we carried out daily pollen counts according to the standard method adopted by Mr. O. C. Durham, Chief Botanist, Abbot Laboratories. These daily counts have been of extreme value in interpreting hay fever symptoms during the active season. Likewise, they have been valuable in attempting to regulate the dosage of pollen antigen during the hay fever season, particularly in the patients who

were treated by the coseasonal method, when doses of antigen are necessarily very small and injections frequent. The greatest value of daily pollen counts is knowledge concerning the plants producing pollen in the surrounding section as well as the type, abundance, time of appearance and disappearance of pollen in the atmosphere.

#### APPROACH TO ALLERGIC PATIENT

One immediately raises the question of proper approach to the problem of the patient with pollinosis. One dictum deserves emphasis—each patient with allergy must be individualized, both in regard to investigation and to treatment. Workers in allergy recognize the importance of standardized, reliable, potent extracts for skin testing, and they agree that such study is dependent upon minute detailed searching and that considerable time and effort are necessary to secure satisfactory results. The average physician feels that he cannot afford the outlay of materials for allergy investigation, nor does he have time for complete allergy investigations. Failure usually results when investigation is carried out with a limited number of allergens that were purchased as a special offer by some commercial supply house, and again failure in therapy results in the average patient who has received the 12, 15 or 20 injections supplied by the commercial house as an adequate pre-seasonal method of pollen hyposensitization. It is therefore imperative that further plans of study and treatment in these hay fever and asthma sufferers are necessary. We believe that the results gained by the concurrent efforts of a completely equipped diagnostic unit with the patient's private physician should result in an increase in the number of patients who secure satisfactory relief of symptoms.

The all-important question of etiology reaches a pinnacle in the consideration of seasonal hay fever and asthma. Frequently the multiplicity of offending factors and the determination of their relative importance is the keynote in the plan of treatment. There is no substitute for complete and thorough

investigation of these patients, and we feel that a definitely higher percentage of good results will be the reward if this procedure be made imperative.

A carefully detailed history relative not only to the present illness but also a general systemic review, should always be recorded. By contact with a large number of patients and a constant review of their histories, one realizes the many and varied factors which may influence the future health of the hay fever patient. If these essentials are recorded in a carefully taken history, they serve as the guide posts to the most advantageous procedures to be followed in the solution of the individual's problem. Every patient should have a complete physical examination, routine laboratory work which includes a red and white blood cell count, a differential count, blood Wassermann, blood sugar determination and urinalysis. The red blood cell sedimentation rate is indicated if any suspicions are aroused that an infectious process may be present in conjunction with the allergic state. The close relationship between the upper and lower respiratory tract in itself justifies a routine x-ray examination of the chest. Consultation with a nose and throat specialist and the conservative corrections of obstructive nasal conditions should never be omitted. Mechanical barriers such as a deviated septum, spurs and nasal polyps will prevent a satisfactory response to immunization. It is true that no intranasal surgery should be carried out until the allergy is definitely under control, but after control is established, any opportune time may be elected for well-chosen surgical procedures.

The choice of the method of skin testing is a matter to be decided upon by the allergist after the completion of the preliminary examination. Some workers limit themselves to only one technic while others use both the scratch and the intracutaneous methods. A certain number of skins "flare" to all substances used intracutaneously and therefore it is impossible to interpret reactions. There are also a number of skins which fail to show any reaction whatever to the scratch method and necessitate the use of the intracutaneous technic.

## THERAPEUTIC METHODS

In pollen allergy, sensitivity to pollen is the largest factor. Only a few patients have the opportunity of visiting pollen-free areas and it is obvious that one cannot eliminate the pollen of hay-fever-producing trees, grasses, and weeds. Desensitization to the specific offending pollen therefore is imperative. Is it acknowledged among workers in allergy that pollen desensitization by the accepted methods will give 90 per cent of sufferers an adequate relief of symptoms? What methods are to be adopted to carry out therapy which results in such excellent clinical relief? It has been noted previously that each patient must be individualized, both as to investigation and to therapy. Complete survey of the patient's problem is necessary; this includes not only tests for pollens of suspected trees, grasses, weeds, but also a careful interpretation of the allergens other than pollen, and strict adherence to the prescribed routine of elimination or desensitization. Occasionally, we have seen a patient with seasonal hay fever and asthma who could not be desensitized, but who had very little discomfort during the pollen season because he had strictly eliminated all epidermal, inhalant and food substances to which he was found sensitive. This is not the method of therapy to be advised, but it does illustrate the point that allergens other than pollens play a part in the production of patients' symptoms. For this reason, we stress the advisability of a strict allergic regimen, particularly before and during the active hay fever season.

Three methods of therapy may be used in desensitization procedures—coseasonal, preseasonal, perennial.

**Coseasonal Desensitization.**—The patient who is seen at the onset or in the middle of the hay fever season and who has had no form of therapy presents a difficult problem. For many years, it was considered undesirable to begin treatment during the active hay fever season, but in recent years, many workers have adopted a plan of coseasonal treatment which is devoid of any danger to the patient, and results in satisfactory relief of symptoms in from 60 to 70 per cent of the cases. The

first procedure with the untreated patient suffering acutely with hay fever and asthma is to completely investigate the allergy, prescribe a strict routine, limit activities, prescribe mild symptomatic measures and institute very small doses of pollen antigen at frequent intervals. The doses of pollen antigen under these circumstances deserves more than a casual note. The initial dosage should be from 5 to 30 pollen units (0.05–0.3 cc. 1:10,000 solution) with repeated injections at one- or two-day intervals, gradually increasing the dosage to not more than 80 to 100 pollen units. As the season advances, an optimum dosage of 150 or 200 units may be used, but in our practice, we never use more than this amount. Such minute doses of antigen given two to three times a week will result in excellent relief of symptoms. More care should be exerted and smaller dosage should be administered if one is dealing with hay fever and bronchial asthma. The asthmatic tends to get an overdosage very easily, with consequent intensification of symptoms.

**Preseasonal Desensitization.**—Most physicians use the preseasonal method of desensitization. The patient reports to the physician two, three, four or five months before the expected hay fever season begins. Allergy tests are made and treatment is carried out with pollen extract based upon the patient's history, results of skin tests and knowledge of the patient's environment. Treatment is instituted with small doses of pollen antigen, 10 to 30 units and the dosage is increased at each injection unless an undesirable reaction is obtained, until an optimum dosage is reached for the individual patient. This is usually between 3000 and 6000 units of pollen antigen. With the onset of the hay fever season, the dosage is decreased to approximately 2000 to 3000 pollen units, and maintained at this level until the active pollen season ends. The inoculations are given at intervals of twice a week until a substantial dosage is obtained and then continued at weekly intervals until the close of the hay fever season. With the preseasonal method of treatment, excellent results are obtained in from 70 to 80 per cent of cases.



**Perennial Desensitization.**—Today, many workers are advocating the perennial method of desensitization in the treatment of pollen allergy. A close analysis of opinion concerning this method discloses no points of disfavor and many advantages. Briefly, the advantages may be stated as follows:

1. Intensive preseasonal or coseasonal treatment is avoided.
2. The tendency toward unfavorable local or systemic reactions is decreased.

3. Contact between patient and physician is established and maintained throughout the year. The value of this feature can hardly be overestimated. Many deviations of a patient's health from normal may be corrected in the early stages if he is under the close observation of a physician. We have also found it opportune in a number of patients taking the perennial method of therapy to institute other measures of desensitization, particularly to house dust in the domestic and to bacterial vaccines in the patients who exhibit a definite tendency to upper respiratory tract infections during the fall, winter and spring seasons. Because of climatic conditions during winter months, Cleveland and the surrounding sector offer splendid opportunities for therapeutic measures directed toward controlling respiratory conditions. Every effort expended in this direction promises a more normal state of health and, indirectly, more satisfactory results with allergy control.

4. Treatment may be instituted at any time of year; this enables the physician to distribute his work more evenly throughout the year and to avoid a preseasonal or coseasonal rush of hay fever sufferers.

5. Perennial desensitization permits the patient privileges of vacation and travel. Most patients seek vacation during the summer or early fall months when pollen is heaviest in the atmosphere. The perennial method of therapy presents a convenient aid to the patient in this respect.

6. The final point of advantage and probably the one of greatest significance in control of pollen allergy, is that the perennial method of desensitization offers some promise of a permanent immunity. One does not work with hay fever and

asthma patients for any length of time before he realizes that this is the point of interest to the patient. That permanent immunization can be effected in a large percentage of patients if thorough and consistent therapy is carried out is beyond any pale of doubt. Walker<sup>1</sup> reports cures in 26 per cent of his patients after preseasonal treatment extending over a period of years. If excellent results are obtained with preseasonal desensitization over a period of years, perennial treatment should yield equally good or superior results. Observation of a large group of patients receiving the perennial method of therapy over a period of years will answer this question.

A certain percentage of patients with pollen allergy report for allergy investigation during the fall and winter seasons for hay fever, asthma or some other allied allergic state and begin the perennial method of therapy. However, the majority of patients enter the all-year method of treatment after an intensive preseasonal or coseasonal course of therapy has been followed. Instead of discontinuing dosage, the patient continues to take pollen antigen injections at weekly intervals, the dosage being gradually increased to a maximum level which may be any amount between 3000 and 30,000 pollen units, depending upon the individual case. It is agreed that the results in an individual problem do not depend upon giving a large amount of pollen antigen, but rather upon the reaction of the patient to immunization procedures, regardless of the amount of antigen employed. Injections are best continued at weekly intervals through the first year of therapy. Less frequent intervals may be employed in the late years of pollen therapy, but the interval should never be greater than two weeks. In this respect, we differ with the commercial supply houses, who are extensively advertising their pollen extracts for the perennial method of desensitization, and advising that injections be given once a month. Satisfactory immunity cannot be obtained with such infrequent injections.

Certain points should be emphasized in regard to the technique of pollen therapy. Too severe local reaction or any sign of symptom of systemic reaction should be avoided. Signs and

symptoms of constitutional reaction indicate shocking of the tissues and not stimulating immunity. It is far more advantageous to give a subreaction amount of pollen antigen throughout the course of therapy than to encounter one general reaction. If such a reaction occurs, the dosage should be decreased to a safe level, several injections of this amount being given and then the dosage should be gradually increased again.

The possibility of giving the pollen extract intravenously should be avoided. By careful aspiration of the syringe after the needle is placed in subcutaneous tissues, this possibility as a rule, can be entirely eliminated, but occasionally an error in overdosage is made. Immediately, a tourniquet is placed above the site of injection; a 1:1000 solution of adrenalin is injected in and about the site where pollen antigen was given and small amounts of epinephrine are injected into the opposite arm. After a few minutes, the tourniquet is slightly loosened for a few seconds and then reapplied. The tourniquet is alternately tightened and loosened for a period of thirty minutes, permitting small broken doses of antigen to reach the vital tissues. The patient should be kept under observation for a period of two or three hours, and if discharged, very complete instructions should be given to the patient or relative for the use of adrenalin in case a delayed reaction occurs in six, twelve or twenty-four hours. Many serious reactions can be avoided by the use of this simple technic.

Patients who have received injections of pollen antigen should be kept in the office for twenty or thirty minutes in order to observe and control any constitutional reaction. If reactions are to be noted, they will usually occur in this period of time.

The question of securing potent and reliable pollen extracts for testing and treatment purposes arises. Many commercial supply houses offer perfectly satisfactory antigens in standardized dilutions for therapy in the average case. The antigens are usually prepared in groups, such as the "Spring type," the "Fall type" or a mixture of the two. One immediately recognizes the limitations of this type of therapy and the lack of

individualization for each allergic patient; furthermore, no complete allergic survey has been made, and no correlation is possible between the clinical history and suspected allergens. It is conceivable that any method of therapy directed along these lines would result in satisfactory relief in the average patient, but would fail in the patients whose conditions deviated from the normal.

Many physicians have availed themselves of diagnostic allergy units whereby complete investigation may be carried out, treatment sets of pollen antigen may be prepared according to correlation of clinical history, skin reactions to pollens, and a thorough knowledge of the pollen flora in the patient's environs. In this way, not only are more accurate methods used in planning therapy, but the patient is given the opportunity of availing himself of knowledge concerning his own allergic state, and regarding allergic factors discovered in testing, and he is also stimulated to study his allergic problem. Practically all workers in allergy prepare their pollen extracts and supply treatment sets to the family physician; these are accompanied by detailed instructions regarding the administration and suggested schedule of dosage. Such a plan of cooperation between the allergist and family physician assures the patient of keener interest in his problem and ultimately, of more successful relief of symptoms. In the past three years, we have followed this plan of cooperation with the family physician in more than 300 patients. Results in this group of patients have been very gratifying, and a high percentage have secured satisfactory relief of symptoms. It is needless to state that the average hay fever sufferer is dependent upon his family physician for ultimate control of his problem and we believe the results obtained by the concurrent and cooperative efforts of a central diagnostic allergy unit with the patient's private physician will lead to a better knowledge and control of the pollen allergy problem.

Regardless of every effort, a certain percentage of patients will be found who have discomforting hay fever and asthma symptoms during the most severe days of the pollen season.

A discussion is incomplete without some mention of measures to afford relief of the acute symptoms.

If the patient has rather acute symptoms, the following measures should be considered. Limit activities, avoid undue exercise, heat, fatigue, stay out of the country, off golf courses, by all means avoid swimming and do not drive more than necessary. Eat lightly, carefully check the diet for known or suspected food allergens. If any uncertainty exists, eliminate common food allergens such as wheat, eggs, milk, potatoes, tomatoes, etc. Insist on normal gastro-intestinal elimination. Avoid flowering plants; check house for any possible flowers and remove these and have the room thoroughly cleaned. Avoid contact with house dust and smoke-congested rooms. Remove from environment any known or suspected epidermal or inhalant allergen. Beware of cosmetics, use the nonallergic brands of cosmetics that can be obtained at any good pharmacy. In effect, keep in mind that any substance may be aggravating the patient's symptoms.

Drug therapy is necessarily limited, and when employed should be mild.

Eye drops of the following composition are helpful:

R		
Holocain hydrochloride.....		gr. ii
Zinc sulphate.....		gr. $\frac{1}{2}$
Adrenalin 1 : 1000.....		3 i
Distilled water.....	q. s. ad	3 i

Sig. 2 to 3 drops in each eye three to four times a day.

Eye washes of boric acid solution or normal saline serve to relieve the average sufferer. If edema of the conjunctiva is marked, 10 drops of a 1:1000 solution of adrenalin added to an eyecup of normal saline solution gives good relief. Shaded glasses are quite helpful. Ice-water compresses applied to eyes several times daily will allay irritation and give a sense of comfort.

The nasal passages are best untreated unless symptoms are severe. In this case, a nasal spray of 1 per cent aqueous solution of ephedrine sulphate with 5 grains of metycaine to 1

ounce, is helpful. If the patient is irritated by ephedrine, it is best to resort to a weak solution of cocaine, such as 2 per cent cocaine hydrochloride which is used as a nasal spray. Under no circumstances is local nasal medication to be used unless the patient's discomfort demands such therapy. Oily solutions such as nose drops are as a rule irritating. It is always advisable to use an atomizer in order to secure a more uniform distribution of the medicament to all surfaces.

For oral administration, preparations of ephedrine, atropine and aspirin are commonly used. Before prescribing drugs, the patient should be carefully questioned as to knowledge of any drug sensitivity. It is easily recognized that oral administration of any drug in doses that will not produce toxic effects can be of only limited value to the patient who has severe hay fever or asthma. In our experience, drug therapy by the oral method is of little value, although one may find the exceptional patient who responds nicely to small amounts of the drugs mentioned above.

When the patient with pollen asthma is acutely ill, bed rest is imperative. All of the preceding cautions should be exerted fully, particularly the necessity for a liquid or light diet, plenty of hot drinks, good gastro-intestinal elimination, care of any possible inhalant or food allergens. Ephedrine or ephedrine and amytal may control the paroxysms. The use of a 1:1000 solution of adrenalin hypodermically, as necessary, or the use of the newly marketed adrenalin 1:100, inhaling the fine mist from the nebulizer is indicated in the more severely ill patients. There is no advantage in withholding adrenalin, permitting the patient to suffer one paroxysm after another because this tends only to exhaust and weaken him. A small dose given in the early stages of an attack will prevent many severe paroxysms. In our experience, morphine is usually disastrous, atropine is contraindicated in almost 100 per cent of the cases, and iodides are of questionable value in the acute stage. The same is true of preparations of calcium. Mild sedation is indicated in the average patient since it removes some of the restlessness and anxiety. The best form of therapy

is the institution of investigation and control of the patient's allergic problem to prevent such a recurrence in the future.

### CONCLUSIONS

1. The treatment of hay fever in general practice should be under the direction of a well-trained allergist.
2. The patient should have a complete and thorough investigation.
3. The general practitioner is the ideal connection between the central diagnostic unit and the patient with hay fever.
4. A plan is outlined which has been a great aid in gaining the close cooperation of the patient.
5. The most common cause of failure in the treatment of hay fever is the presence of other unrecognized sensitivities in the patient.
6. The innumerable forms of nonspecific therapy are rapidly being discarded with the further development of specific treatment.
7. The early inauguration of the allergic management of patients with hay fever offers the only assurance of the control and prevention of bronchial asthma as a complication of hay fever.
8. The three methods of treatment of pollinosis are discussed—coseasonal, preseasonal and perennial. Our observations lead us to believe the perennial method to be most efficient.

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## FOOD ALLERGY IN MILD AND SEVERE CYCLIC VOMITING

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IN 1882 Gee<sup>1</sup> published a paper entitled "On Fitful or Recurrent Vomiting" and presented the results of his studies of 9 children suffering with this condition. His opening statement may well be quoted: "These cases seem to be all of the same kind, their characteristic being fits of vomiting, which recur after intervals of uncertain length." Little did he perceive the interest and study that this symptom-complex would command in coming years, nor the controversy that has arisen among workers concerning etiologic factors. Gee described the outstanding symptom, vomiting, and noted the lack of periodicity of attacks. He also called attention to the presence of clay-colored stools during the attacks in some cases.

Recurrent vomiting is classified as a disease of the stomach by many textbooks. It is not a disease, particularly not of the stomach, but it is a symptom-complex in which the majority of symptoms are manifestations of gastro-intestinal disturbances, the etiology of which is obscured by the lack of knowledge concerning the assimilation of faulty metabolic products, the mechanism of absorption and the means by which such a profound toxemia is produced in the body. That recurrent vomiting in children is a result of a profound toxemia is supported by many points, evidenced by symptoms, physical findings and the clinical course of the patient.

Cyclic or recurrent vomiting occurs frequently, although the true nature of the condition often is not recognized. The condition is characterized by recurring attacks of vomiting, which occur at regular or irregular intervals of days, weeks, or months, being initiated without any adequate exciting cause,



and terminating spontaneously, leaving the patient in a state of profound prostration. The duration of the active stage characterized by vomiting, fever and prostration is usually one, two or three days, although the prodromal period and the period of recovery lengthens the attacks to three, four, five, six or seven days.

This condition occurs with equal frequency in boys and girls. The onset is usually between the ages of two and four years, but may date back to infancy. The physical characteristics are often distinctive, denoting a delicate constitutional make-up, a highly nervous temperament and a tendency to lack of muscle tonus with increased vasomotor reactions. Much has been said of the inherent neurotic tendencies indicating characteristics as noted above. Certainly, one can recognize a more sensitive, nervous response in these children, and often one can elicit the possibility of a functional background in the parents.

The symptoms are typical. The prodromal stage is characterized by anorexia, lassitude, rings under the eyes, irritability and a sense of discomfort in the epigastrium. After a period of from twelve to twenty-four hours, there occurs the active stage of extreme nausea, vomiting, elevation of temperature, prostration, abdominal discomfort, constipation or diarrhea. Vomiting occurs at frequent intervals, usually from one-half to every three or four hours. The vomitus is usually composed of mucus, it is stained deeply with bile and occasionally it is blood-streaked; this apparently is due to the violent emesis. The temperature is elevated and may rise to 104° or 105° F. Within twelve to twenty hours, the exhaustion is quite marked, dehydration is noticeable, and stupor is apparent. Then recovery begins, but is drawn out over a period of a few days, this stage being marked by apathy toward food and by fatigue and languor. Between attacks, the child enjoys normal health except for mild gastro-intestinal symptoms such as epigastric cramps and constipation, fatigue, and a constantly variable appetite.

Physical findings other than prostration, fever, dehydra-

tion, tachycardia, hyperpnea and pallor are few. The abdomen is usually distended early in the course of an attack, but later it is flat, exhibiting generalized tenderness due to violent emesis more than to gastro-intestinal pathology. Examination of the stools in some cases reveals a lessened bile content; mucus is noted occasionally and rarely are there any evidences of blood. Laboratory studies give results of a consistent nature. Leukocytosis is a constant finding. Hypoglycemia, lowering of the bicarbonate content of the plasma, and acetone bodies in the blood and urine have been reported. The urine is necessarily scanty. All findings return to normal with cessation of symptoms and the child progresses in a normal manner until the advent of a similar attack.

Analysis of symptoms in a child with severe cyclic vomiting suggests more than a casual relationship between this symptom-complex in childhood and the occurrence of migraine in the adult. In our series of cases, hemicrania was not an infrequent symptom. In the older children, gastro-intestinal symptoms became less severe and cerebral symptoms more marked in direct relationship to age. In a recent review of cases of migraine, some of the patients gave a history of recurrent attacks of vomiting in early childhood. A more carefully elicited history would probably reveal that an even greater percentage of patients experienced such a symptom-complex in childhood.

No effort is made to explain the mechanism by which protein substances reach the tissues. That there exists some undemonstrable biliary dysfunction permitting the passage of unsplit protein substances into the blood is without question. It is likewise conceivable that there exists an increased permeability of the intestinal mucosa, and with any degree of intestinal stasis or reverse peristalsis, an overload of nonsplit protein substances or faulty metabolic products is thrown into the circulation, reaching the tissues as toxins and producing a violent reaction. That cyclic vomiting is a result of severe toxemia is beyond pale of doubt. The prodromal period marked by anorexia, restlessness, irritability, languor, the early

appearance of fever, the active state characterized by epigastric discomfort, gaseous distention, cramps, colic, often diarrhea, nausea and extreme emesis which lasts from twenty-four to forty-eight hours, and the final stage, with severe exhaustion and profound prostration followed by a slow and gradual return to a normal state within a period of several days, strengthens the contention that such a clinical picture could only result from severe toxemia. What part food allergy plays in influencing the precipitation of this chain of symptoms, or food allergens in rendering the intestinal mucosa permeable to the passage of toxic products to the tissues cannot definitely be determined at this time. Our studies lead us to believe that severe cyclic vomiting is largely influenced by food allergy and relief of symptoms can be obtained with control of allergy.

Because of the results which we have secured in the treatment of 20 patients with cyclic vomiting, we desire to report our findings and to emphasize the importance of food allergy in the production of this symptom-complex.

These patients were referred to the Allergy Department because of the major symptom-complex of recurrent vomiting or for investigation of associated conditions that were thought to be due to allergy. It is interesting to note that a number of these patients were referred from other departments in the clinic, impressions or diagnoses having previously been established without a consideration of recurrent vomiting. Two patients were referred from the Genito-Urinary Department because of impressions that led to diagnoses of recurring pyelitis. Complete investigation between and during attacks did not suggest any connection between the genito-urinary tract and the symptom-complex. Following a complete allergy investigation, a regimen based upon the results of the allergic studies gave complete relief from symptoms. In one case, a diagnosis of intermittent gastro-intestinal obstruction had been made. Complete survey of the patient's problem including roentgen study of the gastro-intestinal tract did not suggest any definite lesion but complete relief was secured following the institution of a regimen based upon the results of our

studies for allergy. A few of these cases were seen originally in the Department of Ophthalmology because the parents believed that eye pathology, particularly ocular muscle imbalance, could produce the symptoms noted. The majority of patients were referred for allergy investigation after other causes had been excluded and in the belief that food allergy might be a large factor in the production of symptoms.

Certainly, the most valuable aid in establishing a diagnosis of recurrent vomiting is a carefully elicited history. The history must include a thorough summary of the nature of the attacks, their frequency, the physical state during and the condition of the patient between attacks, faulty eating habits and any tendency toward nervousness or environmental factors which might have a bearing on the present illness. No less important is the careful inquiry into the frequency, severity of recurring respiratory infections and their relation to attacks. Our experience leads us to believe that respiratory tract infections play a minor rôle in precipitating attacks. A complete review of symptoms which may be due to disturbances in the various systems will be of further aid in establishing or excluding any possible causative influences. We believe that the clinical picture is a very definite one, and that if one follows the trend of symptoms as noted above and evaluates the characteristic physical findings, errors should not be encountered in firmly establishing a correct diagnosis.

A painstaking history regarding the possible presence of allergy, particularly food allergy, is imperative and through this, one may obtain knowledge as to whether or not the patient is an allergic individual. Such positive information is strengthened by the presence of a strong family history of allergy. Certainly, a review of the personal and family history for the presence of any known allergy which is producing cutaneous, cerebral, respiratory or gastro-intestinal tract manifestations will add greatly to the information concerning the nature of the patient's illness and further knowledge relative to causative factors.

The carefully elicited history and thorough physical exami-

nation usually enable the observer to establish a definite diagnosis. However, in a certain percentage of cases, questions arise concerning the possibility of organic lesions, particularly of the genito-urinary and gastro-intestinal tracts. In such instances, more thorough and complete examinations by *x*-ray and other laboratory procedures are necessary to exclude these factors. Likewise, examination of the eyes, roentgenograms of the chest, and any other studies which will exclude any conditions exerting a direct or indirect influence should be performed. In our studies, we include complete examination of the blood, blood sugar, blood Wassermann, urinalysis and often red blood cell sedimentation rate, if there is any suspicion that an infectious process is present.

#### TESTS FOR ALLERGY

It is customary to employ the scratch method of testing for allergens in the majority of cases. By the use of this method, sufficient information may be obtained in a small percentage of patients and certainly one avoids any dangers of constitutional reaction. Workers in the field of allergy grant that only a small percentage of patients will exhibit positive reactions to allergens by the scratch technic, and this is particularly true in patients in whom food allergy is the major problem. In the group of children of sufficient age to permit use of the intracutaneous technic, further investigations with direct testing usually give sufficient information regarding causative factors. We have not experienced poor and unreliable results in testing for food allergy as some workers have stated, but find our results most promising.

In many patients who present the symptom-complex of recurrent vomiting, the age, or mental or physical qualities have prevented the direct methods of testing. In this group of patients, the indirect or passive transfer method of testing becomes indispensable. In our experience, the passive transfer method has been of greatest value where the following conditions exist:

1. In children where physical and mental shock render direct methods of testing inadvisable.

2. In patients with severe cutaneous lesions, where extensive involvement and often lichenification of skin renders sites of injection impossible.

3. In the group of patients who present a generalized hypersensitive, nonspecific response to any substance applied. This response probably is due to trauma and release of histamine-like bodies locally and it is not infrequently seen in cases of eczema and urticaria.

4. In the acutely ill patient.

The passive transfer method of testing presents no technical difficulties. By taking sufficient blood from the allergic patient to be tested; we do not experience any limitation of tests, but on the contrary find opportunity to check questionable or suspected allergens repeatedly. It is obvious that infinitely more time, detail, and flawless technical work is involved in such a procedure. In the 20 cases of recurrent vomiting presented in this discussion, investigation for allergens was carried out by the passive transfer method in 10. Our findings with this indirect method of testing indicate that the results have been equal to or superior to those secured by the direct method of testing.

Finally, one may necessarily use all 3 methods of testing for allergens in order to obtain sufficient information concerning the allergic reactions. Seldom does this combination of methods result in failure, but if such an instance occurs, further investigation through food diary, elimination diets of individual or stock type, and the use of the digestive leukocyte response, as recommended by Vaughn,<sup>2</sup> gives information which is of undeniable value.

Twenty children with severe cyclic vomiting have been treated since January, 1934 and it is interesting that this group comprises 10 per cent of the total number of children treated for allergic disease during this period. This fact, in itself, impresses one with the frequent occurrence of this condition.

The average age of our patients was seven and one-half

years. In several of these patients, symptoms had been present since infancy, and in others the complaints had appeared comparatively recently, the average duration of symptoms being three and three-fourths years. The positive family history of allergy which was found in 13 or 65 per cent of these patients is approximately the same as that in any allergic condition occurring in children.

Fifteen or 75 per cent of the patients with cyclic vomiting exhibited clinical manifestations of allergy. These were allergic rhinitis, asthma, urticaria, allergic conjunctivitis, and eczema. The diagnosis in these cases can usually be established by a carefully elicited personal and family history, physical examination and allergy investigation.

Complete and thorough skin tests with from 120 to 150 extracts were carried out. In 10 or 50 per cent of the cases, the passive transfer method was employed. In cases where limitation of testing was encountered, we have found that the group type of food extracts is valuable.

The physical findings, at the time of the patient's visit to the clinic were negative in 14 instances. Of these 14 patients, diagnoses of pyelitis had been made previously in 2 instances. During the time these 2 patients have been under our observation, no evidence either by laboratory procedures, roentgen examination or complete genito-urinary investigation has been revealed which would substantiate such diagnoses.

Physical examination revealed evidence of associated pathological conditions in 6 or 30 per cent of the total number of patients with cyclic vomiting. Three of these patients had hypertrophied tonsils and adenoids, 1 was suffering from malnutrition, 1 had rickets, and 1 had a deviated nasal septum. In only 7 of these patients, or 35 per cent, did we find it necessary to employ complete gastro-intestinal roentgen studies to exclude any possible organic lesions, and in each of these seven cases, the findings were normal.

The routine laboratory tests were employed. In 9 of the 20 patients, or 45 per cent, the blood eosinophilia varied from 2 to 11 per cent.

It is of interest to note the foods to which these patients were found to be sensitive. As in other allergic states due to food allergy, the foods commonly included in the daily diet are identified as causative factors. Milk, grains—particularly wheat—eggs, white potatoes, chocolate, beans and peas, tomatoes, spinach, bananas, apples and oranges were noted as causative agents in the order named. In no instance was one food alone recognized as the offending substance, although in several instances, the clinical history and the degree of skin reaction definitely indicated that 1, 2 or 3 foods were major offenders. Our efforts in dietary control have been directed toward complete removal of all offending substances for a strict trial period which varied from three to six months, depending upon the individual problems. After clinical relief is obtained, a more liberal type of dietary management is permitted. Such a procedure shows promising clinical results.

Elimination of offending food substances from the patient's diet is one phase of management. Adequate and palatable substitutes is another and deserves more than a casual thought. In outlining the regimen for the allergic patient, we believe that minutely detailed instructions concerning adequate substitutes, planning of menus and recipes for the preparation of palatable dishes are indispensable. In this respect, we utilize the facilities of our Dietary Department and have received favorable encouragement from the patients and parents as well. Certainly, we feel that too much stress cannot be placed on this phase of the problem. When milk is eliminated, not only are suggestions given regarding adequate caloric replacement, but directions are given for the inclusion of generous quantities of calcium, phosphorus and vitamins A and D as long as milk is withheld from the diet. When wheat is eliminated, it is necessary not only to provide adequate and palatable breadstuffs from the grains permitted, but also to insure a sufficient intake of vitamin B through the concentrated vitamin B products. The elimination of wheat curtails the intake of whole grain cereals, one of the largest sources of vitamin B in the child's diet and therefore, these protective substances must be supplied. Our clinical results indicate that these pre-



cautionary measures are of infinite value in providing protection from conditions which are attributed to dietary deficiency.

The treatment instituted for these 20 patients was strict management based on the results of allergy studies and correction of any associated condition that bears a direct relation to the patient's problem.

General hygienic measures with adequate and nutritious diets are employed and normal gastro-intestinal elimination is emphasized. It is of the utmost importance to supply a well-balanced diet with the proper amounts of carbohydrates, fats, proteins, vitamins and minerals to insure proper nutrition and growth while eliminating those foods to which the patient is allergic.

The results of the treatment of cyclic vomiting in these children indicate that food allergy is a large factor in the production of the condition in a high percentage of patients. In 13 patients, or 76 per cent, excellent results were secured, 4 or 24 per cent showed improvement, and in three instances the patients did not cooperate with us. Therefore, all the patients who have followed the allergy regimen have noted excellent or good results.

#### SUMMARY

Recurrent or cyclic vomiting in children is a condition which has been attributed to many etiologic factors.

Our results in a small series of 20 cases lead us to believe that in all instances, it is influenced by food allergy.

We feel greatly encouraged with the results secured in this group of 20 patients with cyclic vomiting and wish to further our observations over a greater length of time and in a larger series of cases in order to evaluate more fully the significance of food allergy in the etiology of this condition.

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## THE TREATMENT OF BURNS

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THE three considerations which should guide our choice of treatment for a burned patient are: (1) the immediate mortality, (2) the permanent disability, and (3) the comfort of the patient. Certain methods of treatment have special merits which make them particularly advantageous in certain types of burns, and in each case, the appropriate treatment should be given so that the patient may not only be rendered comfortable, but may be assured the maximum safety and the minimum permanent disability.

### I. CAUSES OF DEATH FROM BURNS

It has been well established that there are three distinct phases in the patient's reaction to an extensive burn. The first phase is marked by the initial shock and by the diminution of blood volume secondary to loss of plasma from the burned surface. The second phase becomes apparent at the end of the first day and as Aldrich<sup>1</sup> has showed, is associated with the appearance of streptococci in cultures from the burned areas and is marked by a rising temperature and evidences of severe toxemia. The last phase usually begins about the seventh day and is characterized by a temperature indicative of the presence of sepsis which is secondary to accumulations of pus beneath eschars or necrotic tissue.

Glover,<sup>2</sup> in reviewing a series of 310 cases of burns, observed no fatalities after the fifth day. In other words, the third or septic stage is not dangerous to life, although as we shall see later, it may be the most dangerous stage in respect to permanent disability.

Death during the first five days following a burn comes either (1) as the result of the initial shock, (2) as the result of changes in blood volume, blood concentration and blood chemistry, or (3) as the result of toxemia due to absorption of bacterial toxins and products of tissue destruction in the affected areas.

Davidson<sup>3</sup> and others have shown that in the presence of extensive burns, the blood chlorides are consistently lowered and reach their lowest level at about the fifth day. This, Davidson believes, is due to two factors: (1) loss of chlorides in the exudate and (2) an actual retention of chlorides in the tissues. In addition to this, it has been shown by many workers that there is a marked concentration of the blood, the hemoglobin not infrequently rising to 180 per cent, and the other blood constituents, both chemical and cytological, undergoing a corresponding concentration. The nonprotein nitrogen level of the blood rises, not only as a result of concentration, but also as a result of actual nitrogen retention. This retention is probably largely due to the low blood pressure and the diminished blood volume during the initial stage of the burn, but it may also be the result of actual kidney damage due to absorption of bacterial toxins or products of tissue destruction.

The phase of toxemia which follows the initial shock is, as a rule, the most critical period. The temperature rises daily and finally strikes a high plateau which is accompanied by great prostration or delirium. Examination of the blood shows that it has not returned to normal before this phase appears, and generally the patient is exhausted from the shock of the first day and poorly fitted to withstand a severe toxemia. But as the end of the first week approaches, the temperature curve begins to become septic in character with morning remissions, and the general condition of the patient rapidly improves.

## II. PERMANENT DISABILITY FROM BURNS

There is no more pathetic sight than the needless deformity of a child with the contracted scar of a burned neck pulling the chin downward to the chest wall, distorting the teeth and jaw.

and limiting the movements of the head. Most of these deformities can be avoided if the burn is given prompt and adequate treatment with consideration for the end-result and not merely for the patient's immediate comfort and well-being. The contracted scars of burned hands, axillae, face, and neck are most apt to produce serious and permanent disability, but a burn on the surface of any joint may result in serious deformity. The full extent of this deformity often is not apparent for several years until keloid formation and contraction has resulted in marked limitation of motion, joint changes, dislocation of joints, or ectropion as the case may be. The physician who treats the acute injury is too often heedless of the end-result which he may not be called upon to see.

### III. GENERAL CONSIDERATIONS IN TREATMENT OF BURNS

Probably the best first aid treatment for burns is the saline bath which is always available and can be utilized to relieve pain until arrangements for further treatment are made. If the patient is to be treated with tannic acid, oil should never be applied, because this must be removed with ether before the acid is applied and this is a painful process. Morphine should be given at once, the patient should be kept warm, and as soon as possible, fluids should be given. If necessary, they should be given parenterally in order to combat shock and the blood concentration incident to loss of plasma. A subsequent need for fluid must be determined by following the hemoglobin concentration. If the hemoglobin level is high, it indicates a concentration of the blood and, hence, a diminution of blood volume which demands immediate replacement by large quantities of parenteral fluids. It may be necessary to give as much as 7 or 8 liters of saline daily to maintain water balance.

The level of the blood chlorides and urea should also be followed closely, and should the chlorides be diminished, normal saline should be given. The administration of glucose in 10 per cent saline solution intravenously increases the output of urine and is of aid in controlling any elevation of blood urea.

#### IV. THE TANNIC ACID AND GENTIAN VIOLET TREATMENTS OF BURNS

Since the publication of Davidson's work in the tannic acid treatment of burns in August, 1925, this form of therapy has been widely used in the management of all types and degrees of burns. There is no question but that Davidson is correct in his conclusions<sup>4</sup> that (1) coagulation of the devitalized tissue by the use of tannic acid lessens toxemia and (2) tannic acid as an initial dressing has an analgesic effect. In addition, the coagulum prevents loss of fluid and chlorides and is of aid in the prevention of the initial shock. Pain is controlled within a few minutes following the first application of tannic acid, and the toxemia of the first week is diminished by the use of this treatment.

The best results are obtained by spraying a freshly made 5 per cent solution of tannic acid directly on the burned area after the blebs have been opened and the necrotic skin trimmed away. This should be repeated every half hour until a firm coagulum is formed.

Spraying with a 1 per cent solution of gentian violet, as advocated by Aldrich,<sup>1</sup> has a similar action and likewise results in the prompt formation of a protective eschar. An ordinary nose and throat "atomizer" spray is an efficient instrument with which to apply the solution. Working on the theory that the cause of toxemia in burns was a bacterial toxin, Aldrich made cultures from a number of burns and found the streptococcus to be the predominant organism. Gentian violet was chosen in preference to tannic acid because of its coagulant and analgesic effects and its specific bactericidal powers against the gram-positive cocci. In addition to this, it is claimed that gentian violet is less destructive to the small islands of epithelium that persist in burned areas and hence epithelization occurs faster than with tannic acid.

Both tannic acid and gentian violet have antiseptic properties and either, when applied to a second-degree burn, will result in an eschar which will be dry and free from infection. But neither of these agents is capable of preventing the

ultimate development of pockets of pus beneath the eschar in areas of a third-degree burn. Gentian violet has the advantage of being stable in solution and hence can be kept on hand indefinitely, whereas tannic acid in solution deteriorates rapidly and must be made up freshly twice a week. Gentian violet stains the bed clothing and everything with which it come in contact and is hence somewhat inconvenient to handle. Tannic acid, on the other hand, leaves no stain when the eschar is dried. In our experience, there is little choice between the two methods of treatment.

In either the tannic acid or the gentian violet method of treatment of third-degree burns, the temperature becomes septic at the end of the first week and pockets of pus begin to form beneath the crusts. If the crusts are not removed and if the infection is not adequately treated, there ensues serious damage to the islands of epithelium which are so essential to prompt epithelization. For this reason, we have followed the method advocated by Glover,<sup>2</sup> in which the crusts are soaked off in Dakin's solution at the end of the first week. A rise of temperature usually follows moistening of the eschars, but this soon subsides and is never serious. All necrotic tissue should be removed and adequate drainage of all pockets of pus obtained. Hypertonic saline solution (5 per cent) soaks are of great value in cleaning up the infection after the crusts are removed.

#### V. TREATMENT OF BURNS WITH SALINE SOAKS

The constant application of moist saline packs supplemented by hypertonic saline baths, as advocated by Blair, Brown, and Hamm,<sup>5</sup> has great value from the standpoint of promoting rapid healing with a minimum of infection and scarring. Crusts do not form, necrotic tissue is debrided as indicated, and infection and coagulation do not destroy the islands of epithelium that remain. Hence, the wound is clean and healthy, and in several weeks, skin grafting, preferably by means of a split thickness (thick Thiersch) graft can be done if necessary. All cases in which there is an extensive burn

on the face, neck, hands, axillae, or over a joint should have early skin grafts to avoid the contracted scars that follow when the wound is allowed to granulate in and epithelize spontaneously over long periods of time.

As soon as the patient is admitted, if it is decided to treat him by means of saline baths, he should be given morphine, placed in a padded tub filled with normal saline and the clothes and dirt soaked from the burns. Relief from pain will occur within five minutes. If necessary, the patient can be left in the tub throughout the treatment, but as a rule, after an hour or two he can be moved to his bed and the burns covered with perforated cellophan over which normal saline packs are placed. The burned area should be kept warm by electric lights under a cradle. Once or twice a day the patient is moved to the tub which is filled with hypertonic (2 to 5 per cent) saline, and here all crusts and necrotic tissue are soaked off or debrided. The tub should be clean but need not be sterile. If the dressings have any tendency to stick to the wound they may be removed painlessly after soaking in the tub.

Although this method of treatment is ideal for obtaining the best cosmetic and functional end-results, it is obvious that it requires much more equipment and nursing care than the methods which use coagulating substances. In addition, there is more handling of the patient and hence as a rule, more discomfort. For the latter reasons, it is probably best to reserve this method of treatment for those cases in which the important issue is not the preservation of life but the preservation of function. It is our opinion that as compared to the saline method, the tannic acid treatment affords greater comfort and as much safety from the standpoint of mortality but does not obtain as prompt or as satisfactory healing. Saline soaks are of especial advantage in burns of the hands, axillae, neck, face, and over the joints.

## SUMMARY

1. The treatment of shock, the alleviation of pain, and the regulation of water balance and chloride metabolism are the first considerations in the treatment of burns.

2. Deformities from contractures of scars are frequent and permanently disabling complications of burns.

3. The tannic acid and gentian violet treatment is recommended in cases of severe burns when life is threatened.

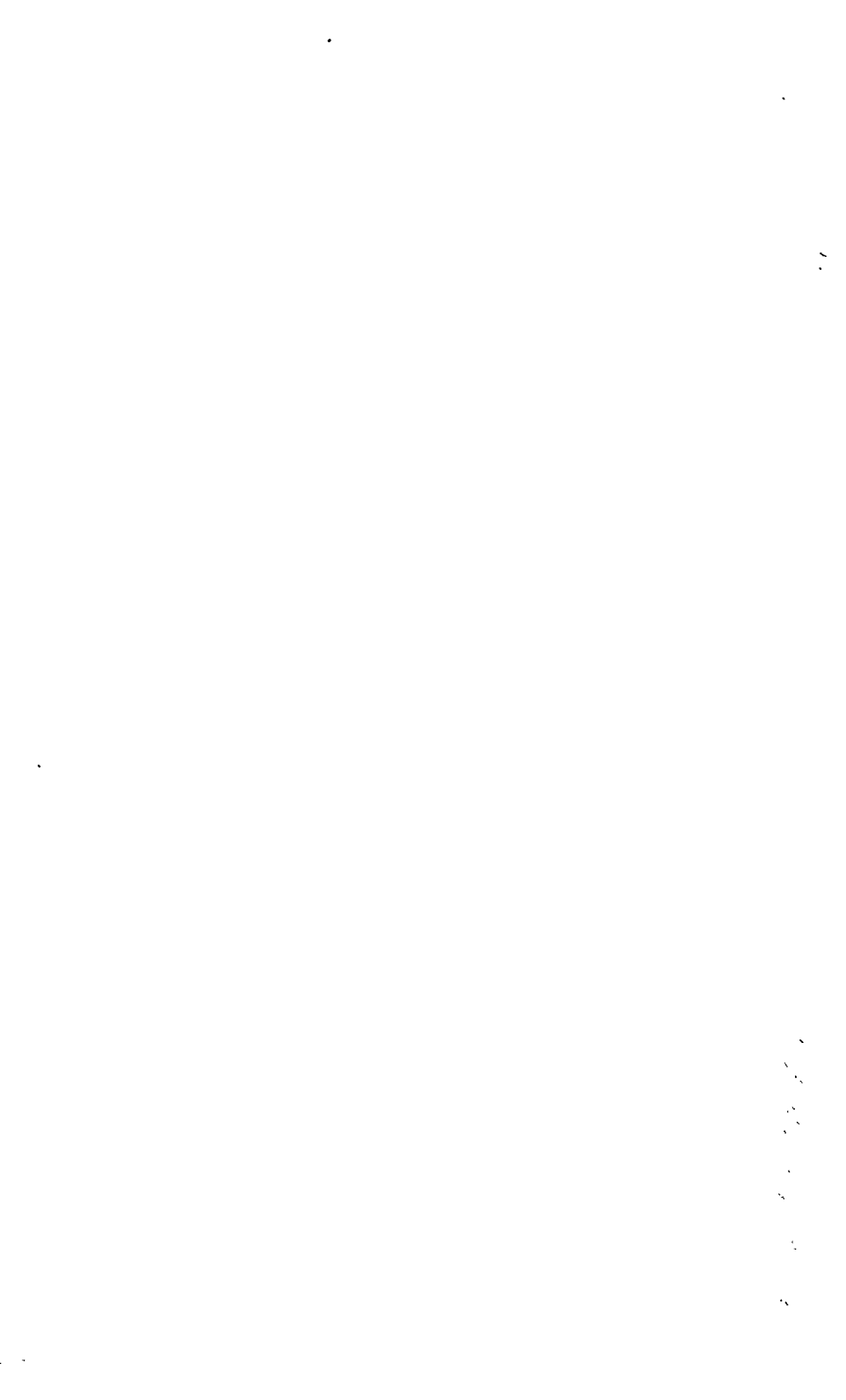
4. With the tannic acid and gentian violet treatment, infection occurs beneath the eschars, islets of epithelium are destroyed, and healing is not so prompt or satisfactory as in the saline soak method.

5. Early skin grafts should be applied following the saline soak treatment in third-degree burns involving the face, neck, axillae, hands, or surfaces of joints, where contractures may result in permanent deformity.

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## ENDOCRINE THERAPY OF BENIGN PROSTATIC HYPERTROPHY

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OUR researches during the past seven years have clearly demonstrated that prostatic hypertrophy in experimental animals may result from endocrine imbalance. Recently, we have shown that this hypertrophy can be controlled by the use of a testicular hormone.

The basis for our belief that this treatment might be efficacious is briefly as follows: there is considerable evidence to indicate that the testes, like their analogues the ovaries, produce more than one internal secretion. Gallagher and Koch<sup>1</sup> made concentrates of bull testes and studied the properties of a substance which has since been isolated by Laqueur<sup>2</sup> and is now known as testosterone. This substance is almost identical in physiological properties with androsterone, which has been isolated from urine by Butenandt.<sup>3</sup> Urinary extracts called "androtin," which contain large quantities of androsterone, have been used by us in clinical and laboratory experiments, and it is now clear that the presence of an excess of this substance will cause prostatic hypertrophy in normal animals. This observation is not surprising, since it has been known for many years that castration of man or animals will cause a marked reduction in the size of the prostate gland. This method of treatment is still employed by veterinarians in the control of benign prostatic hypertrophy in animals. Thus, it seems possible that the etiology of this disease might be related to testosterone production and that the control of the amount of this substance elaborated by the testes would be a possible mode of treatment of benign prostatic hypertrophy.

The production of testosterone by the interstitial elements of the testes is under the control of the gonadotropic hormones elaborated in the anterior lobe of the pituitary gland. We have demonstrated that excess stimulation of the interstitial cells by the gonadotropic substances will result in prostatic hypertrophy and that removal of the gonadotropic hormones by hypophysectomy will cause the testes and hence the prostate to cease functioning and become atrophic.

Numerous experiments<sup>4, 5</sup> indicate that there is an automatic mechanism which normally controls the amount of gonadotropic substance formed and thus maintains the normal level of testicular activity. It appears that a second testicular hormone is produced by the germinal epithelium or some structure closely allied to the tubular portion of the testes. This hormone has been called "inhibin" and is thought to have the property of exerting a controlling influence over the pituitary gland. In the absence of this hormone, the gonadotropic functions of the anterior lobe of the pituitary gland become exaggerated. If the interstitial cells of the testes are still able to function, this could result in prostatic enlargement. Precisely this type of thing might be expected to occur during the involutionary period of a man's life when it is well known that spermatogenesis is retarded and tubular degeneration frequently occurs.

Myers, Vidgoff and Hunter<sup>6</sup> made an observation which indicates that inhibin is not destroyed in the digestive tract and is active when administered orally. They found that desiccated testicular material, when administered to adult male rats, caused prostatic atrophy. We repeated their experiments and confirmed their results. Unfortunately, however, subsequent attempts to repeat this same experiment have not been successful. Nevertheless, after feeding many rats desiccated testicular material in enormous doses for months, we have noticed no effect on the rat other than the atrophy of the prostate in some cases. It was therefore decided to test the effect of feeding small quantities of testicular material to patients suffering from benign prostatic hypertrophy.

Our clinical experiments have been in progress for fifteen months and a group of 76 selected patients has been treated. All of these individuals had definite signs of obstruction such as hesitancy, slowing of the urinary stream, nocturia and frequency. Before treatment was commenced, the patients were completely studied from the point of view of kidney function and endocrine activity. Many patients were hospitalized and their examination usually included complete studies of the blood chemistry, a kidney functional test, a Friedman test, androtestin assay, the basal metabolic rate, cystoscopic examination, intravenous urograms and in many cases, air cystograms for roentgen visualization of the size of the prostate.

These patients were not obviously suffering from endocrine imbalance but there were certain findings which led us to believe that the majority did not possess a normal endocrine system. The basal metabolic rate was almost uniformly low although there were no definite signs of hypothyroidism. According to our theory of benign prostatic hypertrophy, one might expect to find some pituitary involvement. Dr. Perry McCullagh and Mr. Kenneth Cuyler are studying this problem and their unreported findings show that in some cases of prostatic hypertrophy, there may be so much pituitary-like hormone in the urine that a positive Friedman test may be observed which is similar to that obtained in pregnancy.

The majority of the patients treated were not those who had suffered from long-standing obstruction with marked renal impairment as indicated by the intravenous urograms, blood urea and kidney functional tests, which in most cases were normal. Their average age was sixty-eight and one-tenth years, the youngest of the group was fifty-four and the oldest seventy-seven years of age.

All types of hypertrophy were included although we felt that the soft, adenomatous hypertrophies should respond best, and therefore this type of case has been favored in selecting those for treatment.

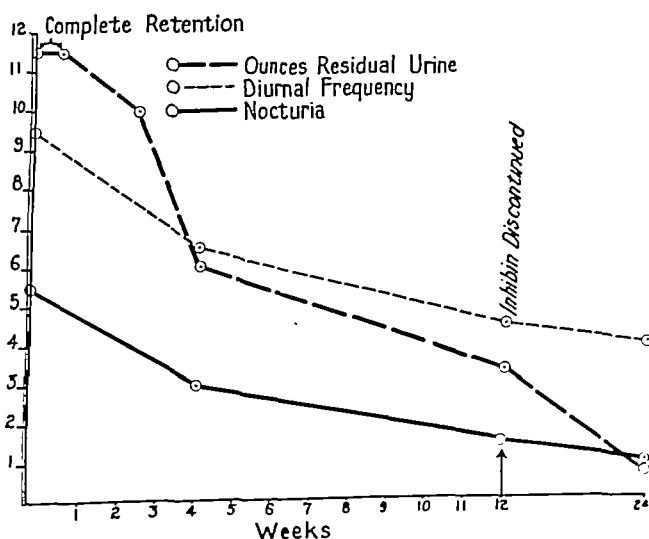
Case I.—The patient was a man, sixty-six years of age, who came to the clinic complaining of complete urinary retention. Two or three years before

this examination, difficulty in urination had begun which resulted in complete retention of five days' duration.

On cystoscopic examination, the bladder neck showed rather pronounced bilateral lobe intrusion and no median lobe was present. The prostatic urethra was markedly lengthened and the lateral lobes met in the midline throughout this distance. Rectal examination revealed the prostate to be quite large but fairly firm.

Laboratory examination revealed the blood urea to be 48 mg. per 100 cc., and in view of the poor kidney function and nitrogen retention, it was decided to use medical treatment.

The patient entered the hospital and to care for the complete urinary retention, he was catheterized twice or three times daily. The capsules were



g. 186.—Chart showing change in urinary symptoms in Case I following treatment with inhibin.

administered and for three weeks no improvement could be noticed. The patient then found that he was able to void a little between catheterizations and his improvement continued until five weeks after inhibin was started, when he was able to empty his bladder completely. He was discharged from the hospital and at that time, the blood urea had returned to a practically normal level and he felt generally much stronger and better. Figure 186 shows this patient's progress in regard to the ounces of residual urine, diurnal frequency, and nocturia.

This patient now feels so well that he considers himself cured; he voids easily and has nocturia only once nightly.

**Case II.**—This patient was a man, fifty-five years of age, who came to the clinic complaining of practically complete urinary retention. A very small amount of urine could be passed and catheterization was necessary twice daily. These symptoms began seven years before our examination and several months before admission, nocturia had become a distressing symptom, occurring every fifteen or thirty minutes.

Physical examination revealed no abnormalities except for the prostate which was markedly enlarged, smooth and of moderate consistency. Cystoscopic examination revealed an obstructive type of bladder and trilobar hypertrophy of the prostate gland with pronounced extravescical bilateral lobe enlargement.

This type of enlargement is that for which prostatectomy would be recommended but also the type in which one might expect satisfactory results after endocrine therapy. This latter method was accepted by the patient and treatment was begun. After ten days, the patient was able to void so well that

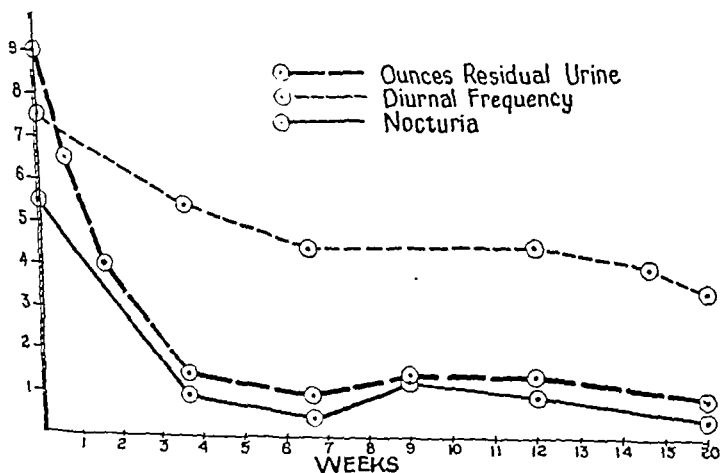


Fig. 187.—Chart showing change in urinary symptoms in Case II following treatment with inhibin.

catheterization was discontinued and three days later, only 55 cc. of residual urine were present when he was discharged from the hospital. Figure 187 shows the progress which this patient made.

This patient has been able to return to his work, is able to urinate almost normally and catheterization yields only a few cubic centimeters of residual urine. Nocturia occurs only once at most and occasionally it is entirely absent.

**Case III.**—The patient was a physician, fifty-seven years of age, who came to the clinic with complete urinary retention which had been present for two days and for which he had resorted to self-catheterization. Symptoms of ob-

struction had begun three or four years before our examination and nocturia from eight to twelve times had been present for the previous six years.

Physical examination revealed trilobar hypertrophy of the prostate of a smooth, soft type; otherwise, the general physical condition was good.

The patient entered the hospital for treatment with inhibin which was administered three times daily. Intermittent and rather frequent catheterization was necessary during the first few days but after seven days, he was able to void so well that catheterization was discontinued and at the time of his discharge from the hospital five days later, he was able to empty his bladder completely (Fig. 188).

When we last saw this patient, he considered himself absolutely well. He was able to void freely and easily with no

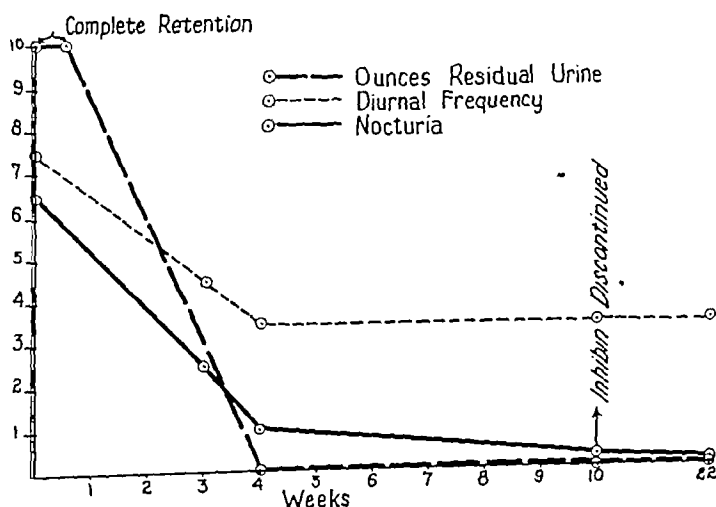


Fig. 188.—Chart showing change in urinary symptoms in Case III following treatment with inhibin.

hesitancy whatever. The voided urine was clear and catheterization yielded no residual urine.

Figure 189 shows another case in which the patient was admitted with complete urinary retention. Treatment with inhibin was begun and nocturia and diurnal frequency were greatly lessened and no residual urine was present after five weeks.

Of necessity, the dose has been empirical since no method of quantitative assay has as yet been developed. For the same reason, it has been impossible to make inhibin concentrates,

or to know how much active material each patient was receiving. Fresh beef testicular material was desiccated in vacuo at 60° C., pulverized and placed in gelatin capsules. Each patient received the equivalent of 60 Gm. of testes daily. This treatment was usually continued for a period of three months. None of the patients received any other type of treatment except in cases of complete retention when the patient was catheterized regularly or an indwelling catheter was used for a time until the patient could void. In the other patients, cath-

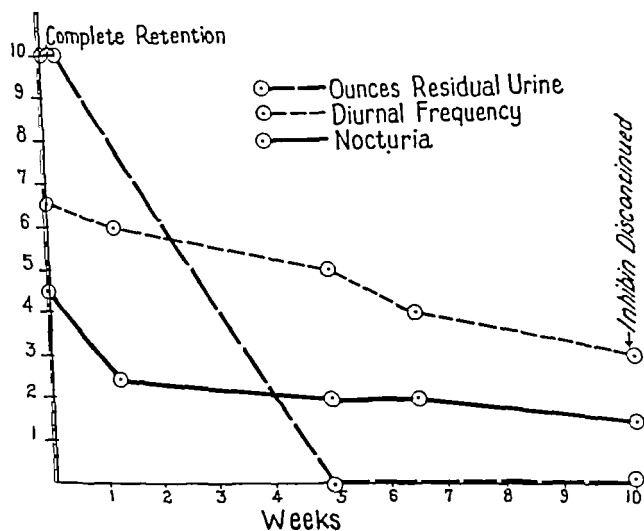


Fig. 189.—Chart showing change in urinary symptoms following treatment with inhibin.

eterization was done only at regular intervals of from five to fifteen days in order that any change in the amount of residual urine might be noted.

In the patients who reacted favorably, the first signs of improvement were usually noted less than two weeks after the beginning of treatment, and maximum improvement was obtained in less than two months. These signs of improvement were decreased nocturia, greater ease in voiding, increase in the size of the stream and reduction in frequency. All patients reported a feeling of general well being.



Of the 76 patients who have been included in this experiment, 48 or 63.1 per cent have had definite improvement in symptoms. As shown in the table, improvement has been observed in numerous types of benign hypertrophy.

The longest duration of symptoms in the improved patients was 2.01 years and in the unimproved patients, 5.1 years.

The reason why 36.1 per cent of the patients did not react favorably to this treatment is not known. It has been stated that 20 per cent of the cases which are diagnosed clinically as benign prostatic hypertrophy are subsequently shown to be malignant. This, no doubt, accounted for some of the failures. One would scarcely expect satisfactory results if the gland has become very fibrotic or if bladder pathology such

	Simple bilateral hypertrophy.	Trilobar hypertrophy.	Middle lobe hypertrophy.	Not specified.
Improved and free from symptoms.	14	17	4	13
Unimproved. . . . .	10	9	4	5
Total. . . . .	24	26	8	18

as marked atonicity or diverticula was present. We have observed failures in treatment following punch operation and cystotomy where there was a sclerotic type of middle lobe and in a case with very atonic and distended bladder and associated diabetes. Possibly greater success will result from this type of treatment when more concentrated preparations of inhibin are available.

The exact mechanism by means of which the improvement in symptoms has been obtained also remains obscure. In our clinical cases, we have no physical or laboratory proof that the prostate has undergone any atrophic changes such as have been observed in experimental animals. These may become more apparent if the dosage is increased or the treatment is

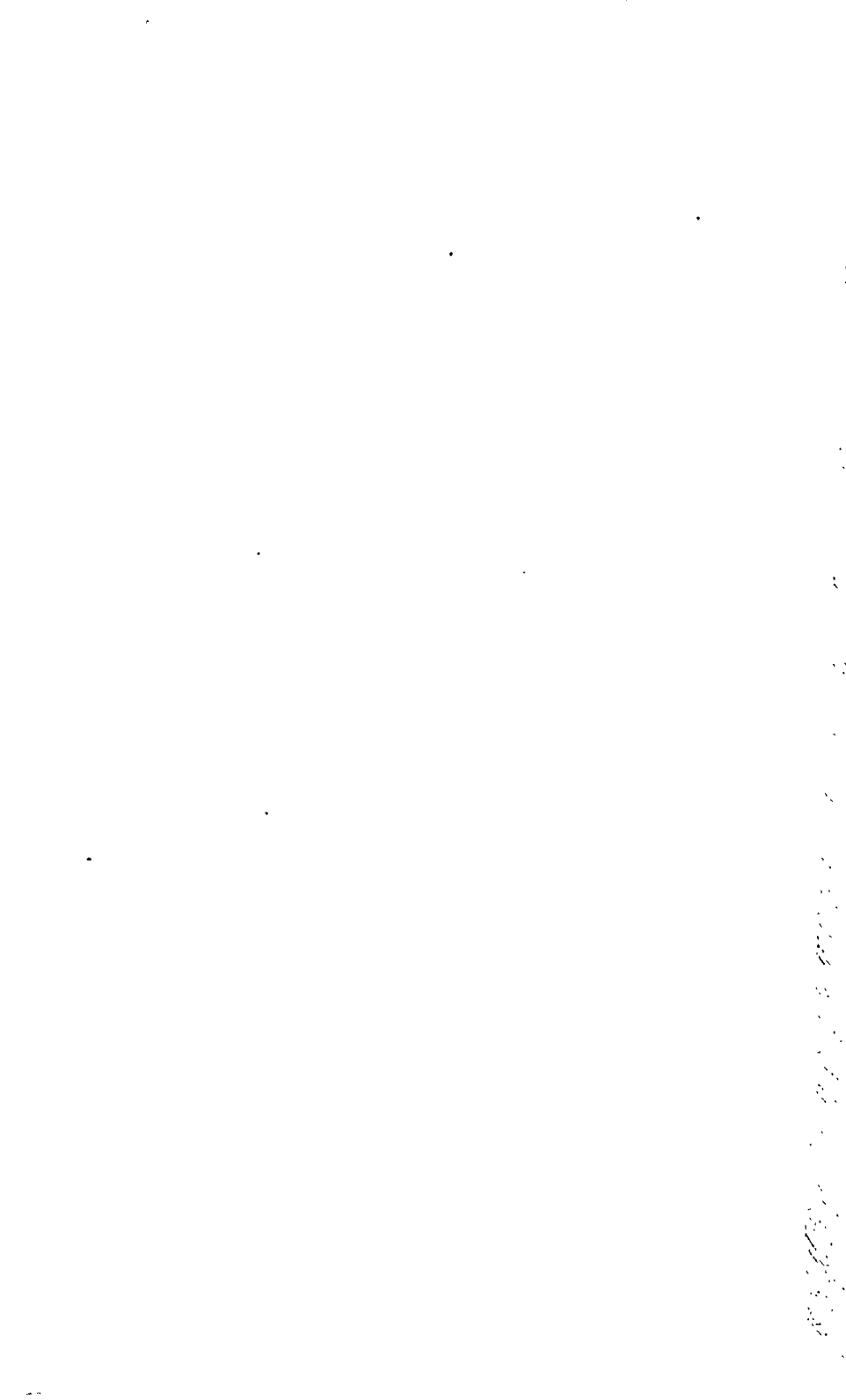
more prolonged. It may be that this group represents a percentage of patients who would improve under ordinary conditions without medication but if this be true, then we have been operating upon too many patients with this type of prostatic hypertrophy. Whether or not this is true can only be settled by more extensive investigation.

### CONCLUSIONS

Laboratory investigations indicated that benign prostatic hypertrophy might possibly be due to a disturbance of normal physiology. Our knowledge concerning the endocrine influences on prostatic activity indicated that the imbalance might be the result of the failure of the testes to produce adequate quantities of inhibin. Seventy-six cases of benign prostatic hypertrophy have been treated with a testicular preparation and in 63.1 per cent they have been relieved of the symptoms for which they sought medical aid.

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## THE SYMPTOMS, DIAGNOSIS, AND TREATMENT OF CYSTITIS

C. C. HIGGINS

THE triad of symptoms usually manifested by a patient with cystitis are frequency of urination, pain and pyuria.

### SYMPTOMS

**Frequency of Urination.**—As a general rule, the patient's attention is directed to the inflammatory process by varying degrees of urinary frequency. Since frequency is a constant symptom, it is likewise an expression of the severity of the disease. In the acute cases, the patient may be required to empty the bladder every fifteen or twenty minutes during the day and night, while in the more mild or chronic cases, the desire to void occurs every two or three hours during the day and two or three times during the night. Urgency and a constant desire to void which is accompanied by considerable discomfort and tenesmus may be pronounced.

**Pain.**—Pain occurs to a varying degree, dependent upon the acuteness of the cystitis. In the presence of retention of urine, more or less constant pain may be felt over the bladder. However, as a general rule, the pain is more severe during the act of urination or it may be terminal in type. In the presence of acute cystitis, severe pain and tenesmus is experienced at the completion of urination, this being aggravated by the patient's straining after the act of urination. The distress is frequently noted in the perineal or over the suprapubic region.

**Pyuria.**—Pyuria may be noted by the patient. The urine may be only faintly cloudy or quite turbid in appearance. In the presence of acute cystitis, the urine may likewise be

tinged with blood and occasionally the bleeding may be quite profuse, suggesting the presence of a vesical neoplasm. However, more frequently a few drops of occult blood may be passed at the end of urination.

In severe cases, general symptoms may also be present such as fever, chills, loss of appetite, nausea, and at times vomiting. The symptoms of chronic cystitis simulate those of the acute process, but are much more mild and less pronounced.

#### DIAGNOSIS

The clinical diagnosis of cystitis is usually determined by a history of frequency, pain and the presence of pyuria. Oftentimes however, the inflammatory lesion in the bladder is associated with inflammatory lesions of the kidney or other parts of the genito-urinary tract. In such cases, conservative treatment alone fails to alleviate the patient's symptoms, and failure to discover the renal condition may lead to loss of renal function and progressive invasion of the kidney by the inflammatory process with ultimate destruction of the renal tissue.

Therefore, in cases in which the patient's symptoms do not subside within a period of ten days or two weeks following adequate treatment, cystoscopic examination, catheterization of the ureters, and the making of pyelograms, if deemed advisable, are indicated. In cases in which conservative treatment is employed, a specimen of urine secured by catheterization should be examined. In women it is quite important to secure such a specimen as a vaginal discharge or blood due to the menses may cause erroneous conclusions to be drawn. In men, the voided specimen secured by catheterization should be collected in 2 or 3 glasses. In the voided specimen, if the urine in the first glass is cloudy and that in the second and third glasses is clear, the cloudiness and turbidity of the urine in the first glass is due to the presence of pus and debris in the urethra. If the urine in both the second and third glasses is hazy, an infection exists in the bladder. Thus, it can be seen that if only one specimen were collected and the urine was cloudy, the presence of bacteria and pus would lead to an

erroneous diagnosis of cystitis, whereas in reality, the inflammatory process might be confined to the urethra. Likewise, routine examination of the urine should be made for the specific gravity, the presence of albumin, sugar, pus, bacteria, blood casts and crystals. As a general rule, the colon bacillus, tubercle bacillus, and gonococcus are found in urine with an acid reaction, while streptococcus, staphylococcus, proteus, and all urea-splitting organisms are found in an alkaline urine. Usually, the infecting organism is found to be the colon bacillus or staphylococcus. If media are available, culture of the urine in glucose brain broth and blood agar is advisable.

Slides are made of three specimens for examination of the sediment:

1. One for routine examination for pus, casts, red blood cells, and crystals. This should be a wet preparation.
2. One is stained by Gram's method for the study of the organisms present.
3. One is stained by the Ziehl-Neelson method for determination of the presence of tubercle bacilli.

Likewise, if a drop of pus can be expressed from the urethra, a Gram stain should be made and carefully examined for intracellular diplococci.

As stated previously, these investigations suffice for the routine study of a patient with cystitis. If, however, no improvement follows treatment, cystoscopic examination is advisable. By this procedure, one is able to determine whether the bladder is being emptied completely, whether an obstructive lesion is present in the urethra or bladder neck, or whether the retention is associated with lues or a tumor of the spinal cord. After inspection of the bladder, a specimen of urine is collected from each kidney for complete study, and pyelograms may be done if advisable.

#### DIFFERENTIAL DIAGNOSIS

As the symptoms of frequency, pain and pyuria are not pathognomonic for cystitis *per se*, but also are symptoms associated with other inflammatory lesions of the genito-urinary

tract, careful interpretation of the findings is essential. Cystitis must be differentiated from pyelitis, pyelonephritis, renal tuberculosis, calculi, pyonephrosis, Hunner's ulcer of the bladder, diverticula of the bladder and urethritis. By cystoscopic examination, ureteral catheterization, and roentgenographic study, the presence of a renal infection can be detected and the presence of such lesions as calculi, tuberculosis, or pyonephrosis can be discovered or ruled out.

Careful inspection and palpation of the urethra as a general rule will suffice to determine the presence of urethritis, polyps or a caruncle, although in certain cases, urethroscopic examination may be necessary. Vaginal examination will reveal the presence of a cystocele, or a thickened ureter due to tuberculosis may be felt. It is always advisable to make a speculum examination of the cervix to determine the presence of erosions and endocervicitis.

In men, palpation of the prostate and seminal vesicles will reveal an enlarged, tender, tense prostate or distended vesicles if the inflammatory lesion involves these structures. Likewise, a history of gonorrhea or instrumentation may be elicited. Pathological lesions in the bladder such as calculi, Hunner's ulcer, trigonitis or diverticuli are ruled out by cystoscopic examination. In uncomplicated cases of Hunner's ulcer of the bladder, the characteristic differentiating symptoms are the marked frequency, both day and night, which Furniss<sup>1</sup> has very aptly described as clocklike in its regularity, and there may be marked dysuria while the urine is clear and sparkling, unless a coexistent infection is present.

Bacteriuria is differentiated by microscopic examination of the urine. In the presence of this condition, numerous organisms may be present in the urine which is free from pus.

If any doubt exists regarding the differential diagnosis due to the fact that so many inflammatory lesions of the genitourinary tract may simulate cystitis, cystoscopic examination should be employed.

## TREATMENT

The treatment of uncomplicated cases of cystitis consists of (1) general measures, (2) internal medication, and (3) local treatment.

In acute cases, rest in bed is essential. A simple diet is prescribed and meats such as beef, pork, ham, and bacon, which contain a considerable amount of extractives, are avoided. Small portions of chicken, veal and fish are permissible. Pepper, salt, mustard, catsup, all condiments and spices should be avoided, as should tea, coffee, liquors and all alcoholic beverages. The patient should drink an abundance of water and milk, at least one glassful every hour being taken.

The bowels should be regulated by the use of mild laxatives. The application of heat by means of an electric pad or hot water bottle to the suprapubic and perineal region relieves the discomfort of the patient.

The medical treatment should seek (1) to alleviate the patient's pain and discomfort and (2) to eradicate the infection. Anodynes should be employed to relieve the discomfort of vesical spasm and the use of codeine internally, or of triple bromides may suffice. Relief may also be afforded by opium and belladonna suppositories which are made of  $\frac{1}{2}$  grain of powdered opium and  $\frac{1}{4}$  grain of extract of belladonna. Likewise, the administration of alkalies may give considerable relief from discomfort. We have found the following prescriptions beneficial:

		Gm. vel cc
R	Sodium bromide.....	30
	Tincture hyoscyamus.....	45
	Elixir simplex.....	q. s. ad 180
Sig. One teaspoonful in a glass of water after meals.		

		Gm. vel cc.
R	Tincture belladonna.....	10
	Potassium citrate.....	30
	Aqua destillata.....	q. s. ad 120
Sig. One teaspoonful in water after meals.		



R	Gm. vel cc.
Potassium acetate.....	30
Tincture hyoscyamus.....	30
Water.....	q. s. ad 180

Sig. Two teaspoonfuls in a little water after meals.

R	Gm. vel cc.
Ext. fld. hyoscyamus.....	10
Liquor potassium or potassium citrate ..	12
Syrup acaciae.....	q. s. ad 120

Sig. One teaspoonful every four hours.

The urinary antiseptic which has been most satisfactory in our hands is urotropin and in cases of colon bacillus or staphylococcus cystitis, it seems preferable to other antiseptics. For this treatment to be efficacious, the reaction of the urine must be acid and this can be accomplished by the administration of from 40 to 80 grains of sodium acid phosphate and urotropin daily and in some cases, larger doses are required to render the urine acid. There is a tendency to administer insufficient amounts of urotropin and sodium acid phosphate and in some cases, 60 to 70 grains a day are required to secure satisfactory results. Likewise, in infections due to the urea-splitting organisms, sodium acid phosphate and urotropin are beneficial. Methylene blue may be administered also in doses of from 1 to 2 grains three times daily, but this has not given as good results. The use of capsules of oil of sandalwood has been satisfactory in cases of cystitis associated with gonorrhea. Pyridium (2 tablets of 0.1 Gm. each, three times a day) is also helpful.

Finally, in the very irritable bladder, we have found that hexylresorcinol, 1 capsule (0.15 Gm.) four times daily or even in larger doses, may give considerable relief.

**Local Treatment.**—During the very acute stage of the disease, we prefer to rely upon medical and palliative treatment as irrigations accompanied by distention of the bladder cause considerable pain. If, however, local treatment seems necessary, instillations of 25 per cent protargol or 16 per cent gomenol suffices. We have found that gomenol is more satis-

factory in relieving the patient's pain. In the subacute or chronic stages, irrigations, a solution of 1:4000 potassium permanganate or 2 to 3 per cent boric acid solution may be used followed by the instillation of argyrol, protargol or gomenol. Irrigations are made daily during the subacute stage and then twice weekly. If ulceration of the bladder is present, topical applications of 10 or 15 per cent silver nitrate solution is helpful. Finally, the ketogenic diet may be employed, especially if a coexisting renal infection is present.

### CONCLUSIONS

All patients with cystitis which does not respond to the usual conservative treatment in a period of ten days or two weeks should have cystoscopic examination and complete urological investigation. Complete comfort can be afforded during the acute stage by anodynes and internal medication.

Uncomplicated cases of cystitis respond to conservative, hygienic, dietary, local and medical therapy.

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## THE DIAGNOSIS OF THE BLOOD DYSCRASIAS IN CHILDREN

RUSSELL L. HADEN

WITH a few exceptions, the blood dyscrasias of the child do not differ greatly from those of the adult. A few diseases such as pernicious anemia seen commonly in the adult occur seldom, if ever, in the child. On the other hand, erythroblastic anemia occurs only in infancy and early childhood, and certain dyscrasias such as true hemophilia occur principally in young individuals. Both the hematological and clinical manifestations of the blood dyscrasias are often exaggerated and variable in youth since the hematopoietic system of the growing child is more unstable and thus more responsive to stimuli than that of the fully grown adult. For this reason, immature forms of both red and white cells appear more frequently in the circulating blood of the child than the adult, so the occurrence of abnormal cells in the child may not have the same significance as in the adult.

In every patient suffering from a blood dyscrasia, we must consider (1) the tissues in which the cells are formed—normally, bone marrow and the lymph nodes, and abnormally, the spleen and other tissues; (2) the tissues in which the cells are destroyed, principally the spleen and other parts of the reticulo-endothelial system; and (3) the circulating blood elements which represent a balance between blood formation and blood destruction. The important dyscrasias are best discussed under three heads:

1. Those involving primarily the red cells.
2. Those involving primarily the white cells.
3. Those involving primarily the platelets and other coagulating elements.

## I. BLOOD DYSCRASIAS INVOLVING PRIMARILY THE RED CELLS

The dyscrasias involving the erythrocytes concern almost entirely the anemias, since polycythemia vera is exceedingly rare in childhood. There are also fewer causes to consider for the anemias in childhood than in the adult although in general, the same etiologic factors must be considered. The following classification is a convenient one to follow in all anemias. This classification emphasizes that the examination of the circulating blood reveals only the balance between blood loss and blood regeneration at the time the count is made. It follows that every anemia is due to increased blood loss, decreased blood formation or a combination of these two factors. The rate of formation is best measured by the reticulocyte count, since this indicates the number of young cells delivered to the circulation and the rate of blood destruction by the amount of bile pigment formed, since this is the end-product of hemoglobin destruction. Unfortunately, the bile pigment formed cannot be measured easily in the bile or as urobilin in the stools, but if there is excessive pigment formation, it accumulates quickly in the blood plasma and can be measured in terms of the icterus index or van den Bergh reaction.

### CLINICAL CLASSIFICATION OF ANEMIA

#### *I. Due to increased blood loss:*

1. Acute hemorrhage.
2. Accelerated destruction of red cells.
  - (a) By toxic factors especially infection.
  - (b) By rapid removal from blood stream in the spleen because the cell is abnormal in shape or size.
    - (1) Hemolytic jaundice.
    - (2) Sickle-cell anemia.
    - (3) Erythroblastic anemia.

#### *II. Due to decreased blood formation:*

1. Quantitative decrease in functioning marrow by aplasia due principally to infections, poisons, or replacement of erythrocytic tissue by overgrowth of myeloid tissue as in leukemia.
2. Quantitative decrease in activity of marrow present especially by infection and other toxemias, cachexia and malignancy.

3. Qualitative decrease in marrow function due to a lack of specific elements necessary for normal red cell formation.

(a) Deficiency in iron due to:

(1) Insufficient food intake or supply by mother during fetal life.

(2) Chronic hemorrhage.

(b) Deficiency in the erythrocyte maturing factor (EMF).

These different classes and causes of anemia may be considered in greater detail. Anemia due to acute hemorrhage in childhood is uncommon but may be caused by trauma or be secondary to a defect in blood coagulation. Rarely there is chronic gastro-intestinal hemorrhage as from an ulcer in a Meckel's diverticulum. The cause of a hemorrhagic anemia is usually apparent. The cells remaining in the circulation are normal in shape, size and hemoglobin content, so the color and volume index is normal as well as the icterus index. Regeneration starts rapidly to replace the lost cells so the reticulocyte count should rise soon after the hemorrhage.

The hemolytic anemias are most interesting. It is especially common for infections to cause increased hemolysis of red cells and so produce a hemolytic anemia. Unless the marrow is depressed at the same time, there is usually a quick response of the marrow to the need for new cells with an outpouring of cells and therefore a rise in the reticulocyte count occurs. If many cells are destroyed, the spleen has more work to do and thus becomes enlarged if the blood destruction continues sufficiently long. With the excessive destruction of hemoglobin, bile pigment is formed beyond the capacity of the liver to excrete it, and the icteric index rises. The cells in the circulation in a hemolytic anemia due to infection are normal.

Congenital hemolytic jaundice, sickle-cell anemia and erythroblastic anemia are all examples of hemolytic anemias in which there is a congenital defect in shape or character of the red cell. Since the cells are abnormal, they are quickly taken out of circulation by the spleen so there is splenic enlargement and a rise in the bile pigment of the plasma. The bone marrow is overactive in trying to compensate for the

excessive destruction, and the reticulocyte count is high due to the many new cells in the circulation. In congenital hemolytic jaundice, the cells tend to be a spheroid rather than a biconcave disk. This should be designated, as suggested by Naegeli,<sup>1</sup> as spherocytic anemia. In sickle-cell anemia, the same conditions hold due to the sickle-shape of the red cells. The characteristic finding in erythroblastic anemia, so designated by Cooley,<sup>2</sup> is the enormous number of erythroblasts in the circulating blood. These are also taken out by the spleen, so the characteristic chain of events in a hemolytic anemia occurs here also. The clinical manifestations in hemolytic jaundice are anemia, jaundice with normal-colored stools, and an enlarged spleen. In sickle-cell and erythroblastic anemia, the anemia and splenic enlargement are the presenting clinical findings.

In the anemias due to decreased blood formation, less hemoglobin is destroyed, so jaundice does not occur. The icterus index is usually lower than normal and the reticulocyte count is low due to the marrow aplasia or replacement. Infections may cause a profound aplasia which usually involves all elements of the marrow so the platelet and leukocyte count are low as well as the red cell count. Other types of cellular toxins, such as arsphenamine, have a similar effect. Leukemic infiltration in the marrow simply crowds out the red-cell forming tissue. Here, the white count and platelet count are usually high except in the leukopenic form of leukemia, when the picture is indistinguishable from aplastic anemia unless qualitative changes such as the appearance of lymphoblasts and immature cells of the myeloid series are found. The red cells in aplasia of the marrow usually show no nucleation or basophilia, and such cells as are present are normal except for a tendency to macrocytosis.

In the anemias due to a quantitative depression, there is decreased activity of the marrow which remains normal in amount. Here, the important causative factors are infection such as in the urinary tract and sinuses, or a general defect in nutrition with consequent failure in supply or utilization of

the substances necessary for blood formation. The rare cases of malignancy in children may produce anemia by depressing the marrow also. Here again, the cells present are relatively normal, the reticulocytes are low and there is no increase in bile pigment formation. Leukocytosis is usually absent. Only the symptoms and signs of anemia form the presenting clinical picture.

The qualitative defects in marrow function in the child concern almost entirely the iron metabolism, as this is the substance most commonly deficient. Here the defect is primarily in hemoglobin synthesis rather than red-cell formation, so the characteristic finding on blood examination is a very low color index. If this continues sufficiently long, the cells become small, and the volume index is low also. The white cells and platelet counts remain normal; the icterus index is less than normal and the reticulocytes are not increased.

An iron deficiency occurs frequently in young infants due to an insufficient iron supply of the mother during pregnancy, or a greater need for iron than can be supplied as in twins. Such an anemia can be produced regularly in experimental animals by giving the mother a diet deficient in iron. If a child is given a diet low in iron, such as an exclusive milk diet for a sufficiently long period, an iron deficiency anemia inevitably develops. A chronic hemorrhagic anemia is primarily an iron deficiency anemia, but this is uncommon in infancy and childhood. There is nothing characteristic clinically about an iron deficiency anemia, although a moderate enlargement of the spleen is not uncommon. It is questionable whether a deficiency in the erythrocyte maturing factor (EMF) ever occurs in childhood.

## II. BLOOD DYSCRASIAS INVOLVING PRIMARILY THE WHITE CELLS

Leukemia is not uncommon in childhood. The disease is much more apt to be acute or at least subacute rather than the more common chronic type seen in the adult. The onset is often sudden with fever, enlargement of lymph glands and



spleen, and rapidly progressive anemia. Petechiae, due either to a platelet deficiency or a toxic effect of the disease on the blood vessel walls, are frequent.

The characteristic blood finding in leukemia is a leukocytosis, with the presence of immature cells of either the lymphoid or myeloid series. The immature white cells are often very young, making it difficult to differentiate between lymphoblasts and myeloblasts. From a clinical standpoint this distinction is of little value, so if there is any question about the type, it is best to simply designate it a "blast" leukemia. Typically, there is more enlargement of the lymph glands in the lymphoid leukemia and more enlargement of the spleen in the myeloid type, although such a clinical differentiation often does not check with the blood and histologic findings.

It was formerly thought that most acute leukemias in children were lymphoblastic, but we now know that the myeloblastic type is also common. The oxidase reaction was once depended on to differentiate the two types with the idea that cells of myeloid origin should give a positive reaction. If the reaction was negative, the cells were designated lymphoblasts, but we now know that myeloblasts do not give a positive reaction unless granules have begun to appear, so the oxidase reaction is of no value in differentiating the two forms of young cells. The anemia is just as marked in the two types although the platelet count is more apt to be low in the lymphoid than in the myeloid type.

An outspoken leukemia may be present without significant glandular or splenic enlargement. Here, there is usually fever, petechiae and often necrotic oral lesions. The diagnosis in such cases is, of course, made only by blood examination or sometimes only at autopsy. The great difficulty in such cases is to differentiate leukemia from the blood reaction occurring in certain infections because an infection may so stimulate the bone marrow as to flood the peripheral blood with immature forms in the absence of true leukemia. If the entire clinical and blood picture does not seem to correlate properly, it is best to be guarded in making a diagnosis of leukemia.

Time and further blood examinations will usually make the correct diagnosis.

The clinical condition most frequently confused with leukemia in the child is infectious lymphadenosis (mononucleosis). Here, there is glandular enlargement and often splenic enlargement with a leukocytosis and the appearance of mononuclear cells in the blood which may be mistaken for lymphoblasts or myeloblasts. The patient is seldom ill; however, hemorrhagic and local necrotic features are absent, and a careful study of the mononuclear cells shows that they are not young forms but simply abnormal forms to find in the circulating blood.

Most difficult diagnostic problems in leukemia are seen in children with a leukopenia. Such cases are not uncommon. Usually, the anemia or the enlargement of glands or spleen is the presenting clinical symptom. The anemia is often extreme, and the leukocyte count may be as low as 1000 with a high percentage of mononuclear cells. If the child does have leukemia, a careful search, especially with concentration specimens, will usually show immature forms characteristic of leukemia. An aplastic anemia will give the same clinical picture, but here the immature white cells should be absent. The correct diagnosis may be impossible, however, until it is made at autopsy.

Agranulocytosis is rare in the child but it may occur. It is the opinion now that most primary cases in the adult are due to some drug such as amidopyrine, which acts as a toxic agent on the marrow, preventing the normal development and delivery of leukocytes. Infection may act similarly.

### III. THE BLOOD DYSCRASIAS INVOLVING PRIMARILY THE PLATELETS AND OTHER COAGULATING ELEMENTS

Hemorrhage without injury or out of proportion to an injury is necessarily due to a defect in coagulation of the blood or to an increased permeability of the capillary walls. Such a pathologic hemorrhage is not unusual in childhood. The three important primary types of hemorrhagic disease

seen at this age period are: (1) hemorrhage of the newborn; (2) true hemophilia; and (3) hemorrhage due to a deficiency in blood platelets or thrombopenia.

Hemorrhage of the newborn occurs only in infants, as the name indicates. It is characterized by spontaneous hemorrhage, usually not later than the second week of life. The bleeding may be from the gastro-intestinal tract, from the site of separation of the cord, or into the subcutaneous or subdural tissues. Relatively few careful blood studies have been made in such cases. The platelets are normal, but the coagulation and bleeding times are prolonged due apparently to a prothrombin deficiency. Transfusion usually effects a complete cure. The development of such a hemorrhage is usually prevented by giving whole blood intramuscularly immediately after birth.

True hemophilia is primarily a disease of childhood, since it is a most serious condition and most children so afflicted die from hemorrhage early in life. The diagnosis of hemophilia should be made only in males. There is usually a family history of abnormal bleeding in the male members of the mother's family. In this disease, the abnormal bleeding is due to a prolonged coagulation time and prothrombin time without quantitative decrease in platelets, or abnormality of clot retraction or bleeding time. The fundamental defect seems to be an increased resistance of the platelets to dissolution, so that the thromboplastin is consequently deficient. Clinically in such cases, hemorrhage from the mucous membranes and true petechiae seldom occur. Hemorrhage into the joints occurs practically always and large hemorrhages into the subcutaneous tissues and body cavities are frequent.

The platelets seem easily depressed in childhood, so purpura due to a quantitative deficiency in platelets is common. We speak of this condition as idiopathic thrombopenia, although there must be a cause for the platelet depression. The condition usually develops acutely with petechiae and bleeding from the mucous membranes, especially from the nose. There is seldom bleeding into joint spaces or body cavities. Often

there is a history of a preceding infection such as one of the acute exanthemata, tonsillitis or pyelitis. Here the essential blood findings are a decrease in platelets with failure of clot retraction and an increase in bleeding time. Such cases are usually self-limited and can be tided over by transfusion. If the thrombopenia and purpura become chronic, only splenectomy will give relief.

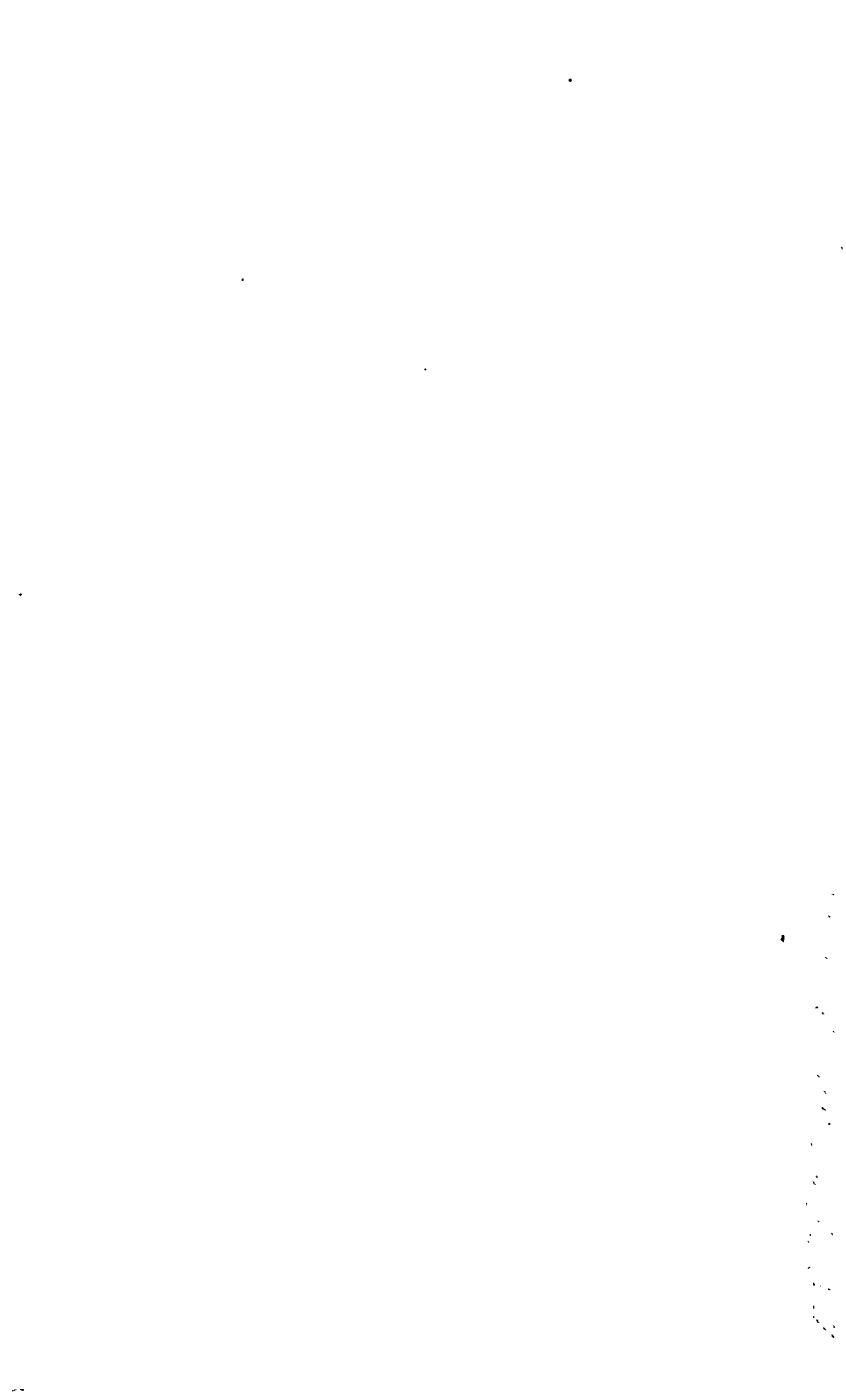
Hemorrhagic disease may also develop secondarily in children, especially the type due to a platelet deficiency such as occurs with aplastic anemia and leukemia, or may occur in the course of some other manifest disease. Likewise, there may be a defect in the clotting mechanism with consequent abnormal bleeding as the result of jaundice or of a deficiency in fibrinogen from liver disease.

#### SUMMARY

The blood dyscrasias of the child do not differ greatly from the dyscrasias of adult life. The blood making and destroying mechanism is more labile in youth, so the response to a given stimulus on the part of the bone marrow, spleen and other parts of the reticulo-endothelial system is apt to be more exaggerated in the growing child. For this reason, greater judgment must be exercised in drawing conclusions from both clinical and laboratory data in the child than in the adult. The dyscrasias are more apt to be acute at this period of life. The diagnostic criteria for establishing a diagnosis of some blood dyscrasias are essentially the same in all age periods.

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## THE TRANSFUSION OF BLOOD IN GENERAL MEDICAL PRACTICE

RUSSELL L. HADEN

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### I. INDICATIONS

THE transfusion of blood is one of the most valuable of all remedial measures employed in general medicine. Every body activity depends on an adequate supply of oxygen and of fluid and food which are furnished only by the blood. Transfused blood supplies the fluid volume necessary for adequate circulation, erythrocytes containing hemoglobin to transport oxygen, protein needed to maintain the proper osmotic pressure within the vessels, platelets and other substances to aid blood coagulation, and antibodies to resist infection, and at the same time, stimulates the bone marrow to greater activity.

In acute hemorrhage, the indication for transfusion is generally absolute. Here, the rapidly reduced volume of blood is usually the most serious phase of the hemorrhage. If as much as one third of the circulating blood is quickly lost, exitus ordinarily follows, since the heart cannot maintain the circulation on the reduced blood volume. In most instances, the hemorrhage is accompanied also by an element of shock. In acute hemorrhage of any magnitude, even without shock, or in a small hemorrhage with shock, transfusion should always be done. The results are usually most brilliant and often life-saving.

In chronic hemorrhage the fluid lost is replaced, so that the total blood volume is returned to normal. Here, the most important element is the anemia. We now know that this type of anemia is primarily an iron deficiency anemia, since this is the one building stone needed for red cell and hemoglobin

formation with a very small reserve supply. As a rule, there is little reduction in the number of cells, but a marked reduction in hemoglobin and consequently a low color index. If the hemoglobin is reduced a sufficient amount and for a sufficient length of time, microcytosis of the red cells develops and consequently the volume index is low.

In uncomplicated chronic hemorrhagic anemia, the administration of large doses of iron such as 60 to 90 grains of Bland's pills daily, will lead to a rapid synthesis of hemoglobin and return of the blood to normal. Such a procedure takes time, however, and often it is more economical for the patient, especially if confined to a hospital, to be transfused, although the iron should be given also to build up the body reserve. In some cases of chronic hemorrhagic anemia, other factors are present which prevent or interfere with the normal formation of hemoglobin, so the expected response to iron therapy of a daily increase in hemoglobin of 1 per cent is not obtained. Here, transfusion may be of great help in stimulating the marrow.

In other cases, an iron deficiency anemia may result from a deficient food supply of iron as on an exclusive milk diet. Not infrequently, there is a defect in absorption or utilization (idiopathic hypochromic anemia) of iron even with an adequate intake. Here also, the response to iron therapy in massive doses is most gratifying and transfusion is seldom necessary unless a rapid return to normal is indicated as in preparation for an operation or to combat other complications such as infection.

In pernicious anemia, transfusion was the mainstay of treatment before the development of liver therapy. We now know that this type of anemia is due to a deficiency in the erythrocyte maturing factor (EMF) formed by the interaction of an intrinsic factor secreted by the stomach on an extrinsic factor supplied by the food. This factor is necessary for the normal growth of the red cell just as iron is necessary for the normal synthesis of hemoglobin. The supply of this factor to the marrow may be altered by liver disease since the liver

is the normal storage depot, or by diarrhea, which prevents absorption.

Since pernicious anemia is a deficiency disease, the therapeutic indication is to supply the missing factor in amounts adequate for the maintenance of a normal blood count for the life of the patient. If the anemia is extreme and is progressing rapidly, transfusion should always be done to tide the patient over the several days that are required before an appreciable effect from liver therapy is secured, even when given parenterally. It is the consensus of opinion, however, that transfusion is of no advantage in the management of the disease except as an emergency measure when the cell count is very low or in the presence of some complicating factor.

In the anemia of pregnancy, transfusion has been found of the greatest value. This anemia is probably a deficiency anemia incident to the pregnant state, so it is self-limited and is cured by restoring the supply of material needed for red cell and hemoglobin formation. The same result is attained, although more slowly, by giving an adequate diet together with iron and liver extract.

In most of the other anemias due to factors which cannot be removed such as chronic nephritis, inoperable malignancy, certain infections, or in such conditions as leukemia, sickle-cell anemia or idiopathic aplastic anemia, transfusion is purely palliative, but is most valuable, since the transfused cells probably live as long as cells made by the patient (two to six weeks) and function normally as oxygen carriers. At the same time, the transfused blood acts as a stimulant to the bone marrow. Even if not curative, transfusion in such cases contributes greatly to the well-being of the patient.

In many toxic conditions, transfusions may be life-saving. In acute poisonings such as by carbon monoxide or bichloride of mercury, the patient may be tided over by the supply of new blood. Transfusion is especially indicated if the bone marrow is involved such as in primary granulopenia (agranulocytosis) which is usually due to the effect of amidopyrine. If the offending drug is withdrawn and the patient tided over,



especially by transfusion, recovery should usually take place. This holds true also for other agents such as arsphenamine or benzol, which injure the bone marrow, but involve predominantly the erythrogenic rather than myeloid tissue, unless the damage to the marrow is beyond repair.

In sepsis with or without anemia, transfusions should always be considered and usually employed. Here as a general rule, there is some decrease in red cells and hemoglobin, and these are replaced by the transfused blood. The bone marrow is depressed in the presence of most infections and is supported and stimulated by new blood. The transfused blood aids in combating the infection by supplying chemical antibodies as well as leukocytes which will function more efficiently than the ones formed in the damaged bone marrow of the patient. Recently, the transfusion of blood from a donor previously subjected to nonspecific protein shock has yielded encouraging results in the treatment of sepsis of different types.

Probably too little attention has been given to supplying blood proteins by transfusion because this is the only method by which they can be supplied if the patient is not making them in adequate amounts. The site of their manufacture in the body is not definitely known, but it is probably the liver; therefore, it is in liver diseases such as advanced cirrhosis that the proteins are not supplied in adequate amounts. If protein is lost through the kidney by proteinuria or into serous cavities as in the abdomen, in the presence of cirrhosis of the liver, or in states of hypermetabolism and excessive intestinal motility such as hyperthyroidism, the blood level is below the optimum level. The only way in which the blood proteins can be elevated quickly is by transfusion, although dehydration increases the concentration without increasing the total amount in the circulation.

In pathologic hemorrhage, there is usually some defect in the mechanism of blood coagulation. The deficiency may be in platelets or in the coagulating ferments. Here again, the only way to quickly destore the deficient elements is by the

transfusion of normal blood. In acute purpura due to a thrombopenia, transfusion is usually necessary to tide the patient over the period while the platelets are low. While the tendency to bleed is permanent in true hemophilia, there are often exacerbations of the hemorrhagic tendency, so frequent small transfusions are often of the greatest help in the management of the abnormal bleeding. Hemorrhage of the newborn which probably is due to a deficiency in prothrombin should always be treated by transfusion. A deficiency in fibrinogen with resulting pathologic hemorrhage can be replaced only by new blood.

## II. METHODS

Theoretically, the most desirable method of transfusion should be one whereby blood to which no foreign substance has been added is given with minimal manipulation and the least possible contact of the blood with the containing vessel or syringe. With a paraffined Kimpton tube, such requirements are met; however, an experienced transfusion team is required for the transfer of blood by this method. In a well-organized hospital such a procedure is possible, and this has been the method of choice by Dr. George Crile for many years and is used routinely on the surgical service in the Cleveland Clinic Hospital.

If the transfusion of blood were done only with a Kimpton tube, the usefulness of the procedure would be greatly decreased by reason of technical difficulties. Fortunately, citrated blood seems to be just as valuable as whole blood and transfusion of such blood can be performed with great ease without especial training or equipment. The citrate method of blood transfusion is by far the most widely used and fulfills all requirements, so it is usually the method of choice. Many citrate transfusions are poorly done in that little attention is given to minimal manipulation, to the gradual addition of the citrate as the blood is withdrawn from the donor, and to the prevention of any clotting whatsoever. Often the blood is allowed to flow from the donor into an open cylinder con-

taining the total amount of citrate needed for the total amount of blood to be withdrawn, stirred vigorously, allowed to cool and then run by gravity into the vein of the recipient. I have long used only a closed container with an attachment for supplying the citrate as the blood is withdrawn. Very little manipulation is required to mix the blood and citrate. Without transferring from the container, the blood is injected by pressure into the vein of the recipient. Many hundreds of transfusions by this method have convinced me that blood so given fulfills every requirement for the satisfactory transfer of blood in all clinical conditions requiring transfusion. The technic of the method mentioned above has been described in detail elsewhere.<sup>1</sup>

If the blood volume is normal and the blood of the donor is normal, the hemoglobin of the recipient should be raised 10 per cent by the use of 500 cc. of blood and the red cell count elevated 500,000 per cubic millimeter. It is apparent that if the anemia is marked, several such transfusions are necessary, since it is seldom advisable to give more than 500 cc. at one time. If several transfusions are to be done, it is far better to give them in rapid succession. I prefer giving them at intervals of twenty-four or forty-eight hours. If the transfusion is given to combat toxemia, sepsis or shock, several are often needed and here also they should be given in rapid succession. In acute cases, it is often desirable to give even two a day employing 200 to 300 cc. of blood at each transfusion rather than 500 cc.

It is most important to type the blood of the donor and recipient most carefully. It is helpful to do this by mixing the cells of each with sera 2, 3, and 4 as well as the serum of each with cells 2, 3, and 4. Cross matching should always be done as an added precaution before the transfusion is carried out. It is usually best to have a donor of the same type as the recipient, but there is never any objection to using a group 4 (Moss) donor for any type. Except in a great emergency, a test for syphilis should always be done on the donor with one of the flocculation tests which are now so perfected.

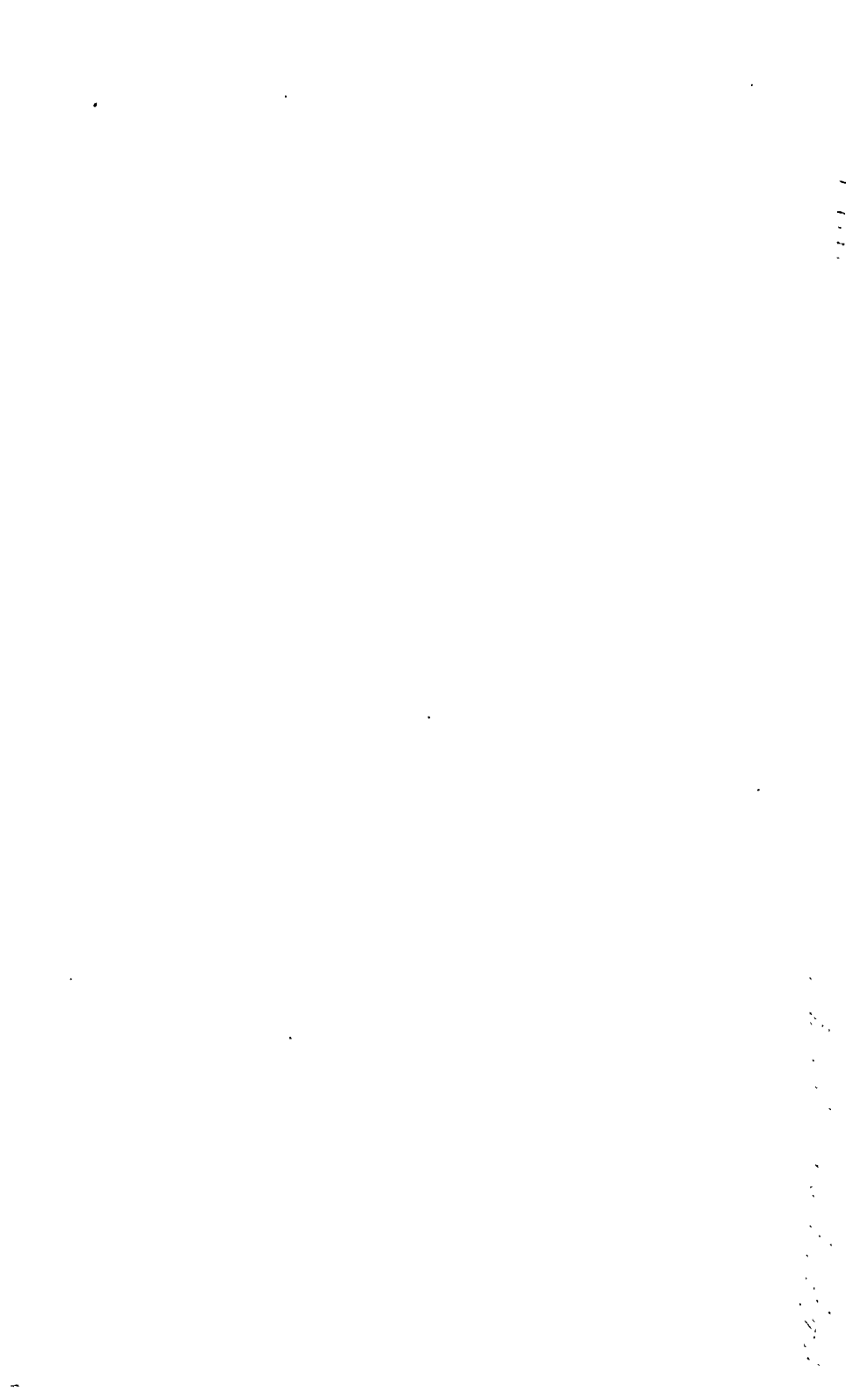
No added time is required for this, as the test can be done while the typing and cross matching are being completed.

### III. SUMMARY

This discussion emphasizes the wide range of usefulness of the transfusion of blood in medical treatment. In any clinical condition in which there is a lack of total circulating blood volume, a deficiency in any of the formed elements of the blood, an insufficient amount of substances dissolved in the substances of the blood, or less than the desired defense against infection, transfusion must be considered. Occasionally, the procedure is life-saving. Seldom, however, should transfusion be employed as a last resort; it should be used when the patient can still respond to the stimulating effect of the new blood. It is most important to give enough transfusions to secure the desired effect because one is often insufficient. If more than one is given, the interval between transfusions should usually be short. If the set-up is available for the transfer of whole blood, this is the method of choice. Citrated blood seems just as effective, however, and the transfusion of citrated blood is so simple it should be available at all times. In general practice, only by making the technic of blood transfusion simple can this most valuable therapeutic procedure have the wide usefulness it deserves.

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## CONSTITUTIONAL PSYCHOPATHIC PERSONALITIES THEIR RECOGNITION, DIAGNOSIS, AND MANAGE- MENT

LOUIS J. KARNOSH

POST-KRAEPELIN psychiatry has been able to draw out of the theological and metaphysical vagaries which obtained for many centuries certain scientifically delineated entities and to establish clear definitions thereof. Particularly has this been true of those disorders which concern the primary intellectual functions involving the phenomena of thinking, memory, association and orientation. Modern psychiatry has yet to deliver into a clear objective light those aberrations which deal with the life of feelings and impulse. Some of these latter disorders are actually in that unhappy position where they are neither accepted by the psychiatrist as true psychoses nor are they wholeheartedly regarded as problems belonging to the moralist and penologist.

Such is the miserable plight of those unfortunates who are commonly called constitutional psychopathic personalities, and whose condition has been aptly labeled "the stepchild of psychiatry." Because it lacks a respectable nosologic standing, it is misunderstood in the clinic, misinterpreted in the schoolroom and maltreated in the courts. Accepted by attorneys only when it offers a legal advantage and scorned by them when it does not, it is largely responsible for the notorious altercations in criminal procedures which at regular intervals give American medical jurisprudence a noisome reputation.

Some psychiatrists have offered the suggestion that the constitutional psychopath does not have a psychosis but possesses a "disease of personality." This appears to be a nice discrimination but is hardly tenable, for by the same token a patient with the "personality changes" of a frontal lobe tumor does not have a disease of the mind but merely harbors a "sick personality."

Such vague synecdoches as "personality" and "constitution" are frank admissions that an accurate concept of this entity is sadly wanting. And yet an entity it must be, for it is as frequently recognized by the practicing physician as it is by the psychiatrist—probably by intuition in both instances rather than by rational definition.

The confusion begins with the very first step necessary to establish an entity—namely its proper nosologic designation. A host of synonyms is employed to designate constitutional psychopathic personality, all of which are bitterly criticized, and no one term is universally accepted. Constitutional inferiority, pathological personality, moral imbecility, hypophrenia, discordant personality, defective delinquent, inadequate personality and a score of other terms contest with an equally large number of appellations which are dictated by the special behavior of the particular patient. In this group we have the recidivist, the pathological liar, the invert, the misanthrope, the pernicious braggart, the unstable, the impulsive, the vagrant type, etc.

When such disagreement exists as to terminology, to frame a satisfactory definition is an almost hopeless task. Stripped of theoretical and speculative elements, setting aside all fine-spun psychoanalytic considerations, and expressing the essential and specific criteria, the following definition is broad enough to include most of the fundamental features. Constitutional psychopathic personality is a condition either hereditary, congenital or acquired, affecting the emotional and volitional rather than the intellectual fields and manifested by certain anomalies of character which make satisfactory social adjustment impossible.<sup>1</sup>

The constitutional psychopath is known better by his deeds than his true defects. A routine psychiatric examination, more often than not, reveals few objective data. Only a perusal of past performance, of a long succession of anti-social acts and society's repercussions to such acts reveals the typical career which brands the individual as belonging to this group.

While terminology is unsettled and definition is difficult,

the average psychiatrist has little difficulty in recognizing this human hybrid. Gathering the common denominators and excluding the rarer variations, a composite portrait of the constitutional psychopathic personality is readily obtained. He is a young individual, generally brought to the consulting room some time in his late teens, who shows little or no concern over his plight because he refuses to recognize he has any aberrations. Showing minimal intrapsychic tension, he appears sure of himself, has a defiant or sulky attitude, is distinctly egotistic and is ready to defend himself at all costs. The long recital by distracted parents of a record of selfishness, repeated petty misdemeanors, outbursts of rage, general instability and impulsive conduct, makes no impress upon his self-esteem, except to bring forth retaliations in the form of wilful lying, clever evasions, frank denial and shallow rationalization.

Training and discipline except for short sporadic periods does little good and the effect of punishment is nil. In addition to a career of instability, shiftlessness, coupled with lack of insight or ethical sense, the personality portrait is embellished with various distortions of the sexual life.

In the face of all this noxious behavior, the ordinary intellectual attainment may be normal or better than normal. Frequently this intellectual development may be spotted or scattered and quite often the superficial impression is gained that the patient is smart if not actually brilliant. A closer study reveals, however, the superficiality of mentation. A lack of inhibition of impulse, an emotional over-coloring of thought and action is sensed as well as an inability to express sound views, adequate summations and conclusions. There is a definite poverty of abstract induction. The constitutional psychopath shows what Kretschmer calls good "free-association thinking," *i. e.*, the ability to handle immediate concepts and percepts with vividness and dexterity, to give expression to thinking which is emotionally loaded. To stem such "short-circuited" mental activity, to draw on stored-up memories and complex association, to make critical and discriminative conclusions and derive broad concepts and thus to make his



behavior less primitive and naïve is beyond his powers. It is here that the constitutional psychopathic personality is defective. No meter stick, no quantitative quotient has yet been devised to measure this deficiency and give it an absolute value. Only by giving the patient free rein and by allowing him to face situations which call for calm deliberation, good judgment and careful analysis, is one able to gain a general knowledge of the fundamental weakness. Since no physical index or quantitative methodology is available to measure this, the temptation arises to call it a defect in the "total personality."

If the orthodox medical mind, which has been properly trained to think in terms of diagnosis, etiology and rational treatment, peruses the literature, the information is garnered that the disease—if it be a disease—is a biogenic one, a disturbance in the deeper structures of personality, a discordance in the impulse life, the temperament and the character elements of the individual. If the physician is venturesome, he can proceed into the elaborate classifications and subclassifications and into the exquisite psychological dissections of Schneider,<sup>2</sup> Kahn<sup>3</sup> and others. Although these writers may claim otherwise, their excellent monographs can only be regarded as more detailed elaborations of symptomatology and serve only to furnish a clearer analysis of where in the psychological matrix the weakness exists, but this must not be mistaken for a true exposition of etiology. The welter of psychoanalytic enthusiasm has produced, as in other conditions, a fine-spun knowledge of how the psychopath performs but not why he so performs.

Boisen<sup>4</sup> has set up a scheme wherein the inadequate personality behaves along certain patterns, these being impelled by a sense of failure as judged by personal standards. Among other things, the behavior is conditioned by the degree of awareness of the inadequacy. From this scheme, it is apparent that the constitutional psychopathic personality has little or no awareness of his defect and the end-results are obvious. Defending his ego to the last ditch, his means of solution are reduced to a few fairly fixed patterns. With an

attitude of flippancy and carelessness, he may find release of tension through clowning, making light of accepted standards and by associating with groups which live at a lower level of responsibility. Here is produced the rounder and the petty thief. He may maintain his self-esteem through constant depreciation of others and appear as the faultfinder and chronic misanthrope. Braggadocio is another method of bolstering self-respect, which sooner or later leads to pathological lying, wherein the delinquent portrays himself as a heroic, muchly abused or misunderstood person. A paranoidal misinterpretation of his troubles is another favorite response. Finally, when acutely assailed he may find temporary respite in self-pity, in claiming bodily ailments or by hysterical explosion. Here attempts at suicide—rarely genuine—amnesias and wandering spells are fugues which serve to help evade the critical situations.

All this is familiar ground to anyone who has dealt with more than two of these individuals. It only serves to make more poignant the problem and at best such exploration of the "depth" psychology offers only incidental and temporizing compromises in the direction of treatment.

Should psychiatry rest on the assumption that the psychopathic personality is an entity that belongs to the realm of depth psychology because of a paucity of physical signs? An expression on this had better be deferred for very good reasons. The rapidly unfolding data revealed by recent studies in cerebral physiology, the amazing growth of endocrinology and its invasions of pragmatic psychiatry, the profoundly significant revelations about human conduct and mental behavior in subjects who have survived removal of brain tissue for brain tumor extirpation and the improved technics of roentgenology, encephalography, and ventriculography are already revealing objective information which gives the problem another and more hopeful approach.

The so-called "personality changes" of fore-brain disease are rapidly becoming crystallized in diagnostic neurology so that they now exact almost the same respect as a positive

Babinski sign or a fixed pupil. The story of Phineas P. Gage is known to every neurologist and with certain reservations this worthy was in every respect a constitutional psychopathic personality for the twelve and a half years he survived his accident.

A number of brilliant resections of the frontal lobe by neurosurgeons have been reported in recent literature. Brickner's<sup>5</sup> observations particularly emphasize that while ordinary intellectual functions are intact, there is a notable defect in the ability to make so-called "complex engrams," to synthesize a large group of ideas, to condense many minor experiences and to express broad judgments. In direct proportion, there is a tendency to more primitive mood swing and franker expression of emotionally colored ideas and impulse components in conduct.

These patients offer good examples of "control" cases in studying the phenomena of psychopathic personality. However, an outstanding difficulty in making fair comparisons is society's attitude. Any person who has miraculously survived an operation for bilateral frontal lobectomy is a very much sheltered and favored individual. He is not called upon to face crucial matters, not exposed to temptations nor asked to make grave decisions. Because the constitutional psychopath has an apparently intact body and a good intelligence he is expected to meet his problems adequately, is given freedom to display the entire catalogue of his deficiencies and when found wanting is punished forthwith.

If we are to give real meaning to the word "constitution," the growth factors involved in this deficiency must be sounded. The most malignant features of the constitutional psychopathic personality appear at the time when there are the greatest spurts in skeletal and visceral growth and when profound changes are taking place in the endocrine system. This suggests the possibility that the psychopath is a resultant of discordant development of all those elements which tend to harmonize the intellectual, emotional and instinctual integrations.

The brain attains its maximum size at the age of seven

years. However, from Flechsig's studies, complete myelinization of certain areas, notably the frontal lobes and parts of the temporal and parietal lobes, does not occur until the years of puberty. It can be inferred from this that the highest mental functions in the most complex association fields do not completely evolve until then. The question naturally arises: can injuries, inflammation or arrest of development occur in these zones and deficiency remain latent for many years before it is recognized or before it flowers into abnormal behavior? A fundamental error in our knowledge of this inadequacy may lie in the fact that cause and effect may be removed from each other by a wide space of time. An injury or inflammation may occur in infancy, leave no immediate after-effects and become relegated in the memory of parents as a matter of little consequence.

The following analysis of 63 cases presented as constitutional psychopathic personalities frankly emphasizes the organogenic approach to this problem.

**Heredity.**—Heredity cannot be ignored as an important contributing factor but because of our inadequate knowledge of human biogenics, no clarified statement can be made. Although in a large number of cases one parent or both were variously described as being irritable, erratic, or unstable, just as often both father and mother were balanced, industrious, socially well-acclaimed individuals. Several were described as being subject to sharp cycling of mood and a fair number were said to have been high-strung, over-refined and specially gifted in certain intellectual fields. Psychopathic personality in other siblings was found in only 2 cases.

**Birth Injuries.**—Intracranial birth injuries are probably more frequent than is ordinarily suspected. Lumbar punctures in newborn infants have disclosed bloody spinal fluid in as many as 40 per cent. Obviously, the vast majority of these injuries are trivial and leave no residue. Injuries over "silent areas" may be extensive and may not manifest themselves until such zones are expected to mature. Even such refined technic as encephalography will not reveal the locus

or the extent of such injury early enough to anticipate abnormal development. Only 1 case of the 63 studied was definitely regarded as a true birth palsy and the encephalogram revealed a porencephalic defect in the left frontal lobe.

**Home Factors.**—Unlike other functional nervous disorders of youth, the psychopathic personality is not essentially a product of the broken or disordered home. Only 5 of the 63 patients could point to gross incompatibility of the parents as a source of irritation, and in only one was this an immediate cause of misbehavior. Jealousy of other siblings is a more outstanding psychogenic component, being noted in over 40 per cent of the cases. Obviously, this must be recognized as more of a symptom of the basic deficiency rather than a true causative factor, for the psychopath is compelled to take advantage of every rationalizing device to maintain his self-esteem. Four of the patients were foster children and here the hereditary component must be given equal consideration with the many psychogenic factors which are bound to emerge with such a social status.

**Childhood Diseases.**—These were found to be no more frequently encountered than in the normal population statistics. However, in more than half of the cases a particular febrile illness was described as being very severe, prolonged and followed by a protracted convalescence. Measles, whooping cough and scarlet fever in the order given were found to be the worst offenders as shown by the following:

*Severe Illness:*

Measles	16
Whooping cough	15
Scarlet fever	10
Empyema and pneumonia	2

*Minor Illness:*

Acute rheumatic fever	2
Chorea	4
Malnutrition	4
	—

Total	54
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No History of Childhood Disease	10
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If anything, infectious diseases are outstanding, not particularly because of their specific nature but because of severity. Measles and whooping cough are not infrequently associated with cerebral complications and a mild encephalitis may be a residue in such infections. Whether or not this occurred in this group cannot be proved but should be regarded as a probability, for the sequelae were found to be not unlike the milder cases of juvenile (lethargic) encephalitis.

**Trauma.**—Injury to the head in early life is a very common incident in the lives of normal children. Trauma to the head occurred in about 12 per cent of the patients in this series but in only 4 can it be said that it was serious. In a fifth the injury consisted of severe burns about the mouth and throat from lye after which the behavior disorders appeared. Injuries to parts other than the head were not included.

**Bodily and Endocrine Developments.**—Some writers have found as many as 40 per cent of these disturbances were associated with endocrine imbalances. In this group 24 were notably dysplastic. Because biogenic assays of endocrine status are as yet difficult and expensive, complete knowledge of this feature of the psychopath is a matter for further investigation. Of the 12 who were more carefully scrutinized in this respect, 10 males were consistently eunuchoid in constitution, and bone growth was ahead of sexual development. All 10 showed a bone age three or four years above chronological age. In contrast, the beard and genitalia were immature. In 6 of these, the male sex hormone assays were low; in 9 the metabolic rate was lower than normal. In all but 1 of the 10 the hypometabolism was regarded as an expression of hypogonadism. Only one had a potential diabetes with a disturbed sugar tolerance.

Twelve psychopathic girls were definitely suffering with hypo-ovarianism and 2 on the other hand were sexually overdeveloped and sexually delinquent. Stealing and lying was the common misbehavior of those with deficient ovarian functions.

This smattering of endocrine study in psychopathic constitution revealed endocrine imbalance in over 38 per cent of the subjects. Partridge,<sup>6</sup> who emphasized this feature, found 26 per cent were so afflicted, while McCartney,<sup>7</sup> who was more impressed by the anomalies of character, believed that only 3 per cent were in this dysplastic group. The theory that in many cases psychopathic personality is an expression of uneven growth seems to have good support and may explain why not a few young psychopaths tend to improve as they grow older because development evens out or compensatory over-function occurs in other endocrine structures.

**Intracranial Disease.**—If all 63 cases had been studied by such methods as encephalography, ventriculography and intracranial surgical exploration, it is possible that some type of encephalopathy would be discovered in a larger number. For various reasons, 22 of the 63 cases were subjected to the above measures, largely because there were neurologic findings justifying such diagnostic technics. Fourteen of these were found to have had positive findings. These were merely gross lesions and no method other than actual brain biopsy can be utilized to discover microscopic changes. Hence, it is impossible to determine how many individuals showing psychopathic constitution actually have true encephalopathy. The findings which are recorded in the table below are striking, not only because of the diversity of the lesions, but also because there is a preponderance of these lesions in the frontal regions and about the neuropituitary portions of the brain stem.

TABLE OF ENCEPHALOPATHIES FOUND IN 22 CASES REGARDED AS CONSTITUTIONAL  
PSYCHOPATHIC PERSONALITIES

Internal hydrocephalus	6
Distention of third ventricle	1
Tumors of frontal lobe	2
Cyst of frontal lobe	1
Atrophy of frontal lobes	3
Chiasmal arachnoiditis	1
Porencephaly in the frontal lobes (birth palsy)	1
Negative findings	7
	<hr/> 22

Naturally when a specific brain disease is established, the diagnosis is changed from that of psychopathic constitution to one of true encephalopathy. In this irregular perusal of 63 cases, 22 per cent were found to have an organic basis in the central nervous system for their unnatural behavior (Fig. 190). If we accept the postulates laid down in reference to

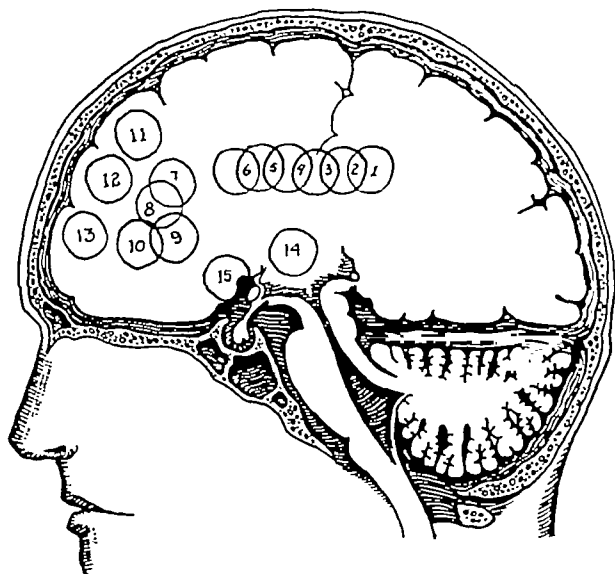


Fig. 190.—General loci of lesions found in 15 cases clinically presented as constitutional psychopathic personalities.

frontal-lobe function it can be said that at least some of the symptoms manifested by these patients are evidences of frontal lobe deficiency.

#### TREATMENT

That organic factors are present in psychopathic personalities is generally conceded. Whether or not these are primary causes or merely contributory elements is not clearly shown. However, these objective findings suggest that treatment should be more than perfunctory and that all psychopathic personalities should not be consigned at once to the custodial scrap heap. As mentioned before, an unknown per-



centage gradually improves spontaneously after growth distortions have disappeared. If there is a history of severe infantile febrile disease, one should try fever treatment with typhoid or other foreign protein. Two patients showed marked improvement after such treatment. Schneider<sup>2</sup> and others have been impressed by the cyclic or periodic activity of the psychopath, and frequently relatives are well aware of the prodromal signs of such cycles. In such cases, the use of bromides and other sedatives may stem a burst of abnormal and impulsive activity. Glandular treatment, when indicated, is to be recommended, but the exquisite diagnosis and therapeutic management of such features had better be turned over to an expert endocrinologist. x-Ray examination of the skull and encephalography, when convenient, should be resorted to, if the faintest suspicion of intracranial pathology exists.

Nobody will deny that the psychopathic personality requires even closer supervision than a psychotic patient. Adjustment to a simple, monotonous routine is impossible because by virtue of his vivid emotionality the psychopath abhors such an existence. Yet under a rigid discipline in an institution this patient is generally normal in behavior.

In most states there is no accepted legal definition of psychopathic personality. This state of affairs does not allow indefinite incarceration of such patients and the vast majority are allowed to run the gamut of reform schools, detention hospitals, prisons and work farms. Until special public institutions for the psychopathic individual are provided, the institutional care of the psychopath shall remain at best a sketchy matter.

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## THE DIAGNOSIS AND NEWER TREATMENT OF GONORRHEAL VULVOVAGINITIS IN CHILDREN

WILLIAM J. ENGEL

IN handling any case of vaginitis in young girls, it is obviously first necessary to establish a diagnosis, and in so doing, to remember that not all cases of vaginitis in children are due to the gonococcus. All cases may be classified as acute or chronic and further subdivided etiologically into the gonorrheal and nongonorrheal forms.

The symptoms in any case of vaginitis may be much the same, consisting of burning or itching and irritation about the vulva and examination reveals a reddened vaginal orifice from which comes a purulent or seropurulent discharge. Not infrequently a urethritis and cystitis may give rise to burning and frequency of urination.

The diagnosis is finally established by careful examination of a smear of the discharge to which a Gram stain is applied. The finding of typical gram-negative intracellular diplococci morphologically identical with the gonococcus is sufficient to establish the diagnosis of gonorrheal vaginitis. Confirmatory evidence may be had by obtaining a culture of the organism, but this is rather difficult to accomplish on ordinary culture media and hardly necessary in most cases.

Acute nongonorrheal vaginitis is occasionally encountered during the course of an acute infectious disease, particularly scarlet fever, influenza and occasionally diphtheria. The latter is characterized by the presence of a membrane while in the others of this type the discharge is very thin and watery and tends to subside spontaneously in a few days.

Chronic nongonorrheal vaginitis may be due to a constitutional disease associated with malnutrition and uncleanness. Also in any chronic vaginitis, it is important to rule out the presence of foreign bodies and to look for parasites in the vaginal canal.

Gonorrheal vaginitis begins as an acute inflammation from which it progresses to a chronic state in the majority of cases. It is usually contracted innocently from infected linens or toilet seats and may be carried directly from an infected parent or nursemaid. Once introduced, the gonococci flourish on the thin delicate mucous membrane of the immature vaginal canal and eventually penetrate deep between the interstices of the epithelial cells into the submucosa, and the inflammation frequently penetrates even to the muscular layer. Fortunately, at the younger ages, Skene's glands, Bartholin's gland and the endocervical glands are not developed, so they cannot harbor the infection. Rarely if ever does the infection travel up to the tubes, but not infrequently there may be an associated gonorrheal proctitis which must be recognized and treated if a cure is to be obtained.

This disease is highly contagious and an outbreak in a children's ward of a hospital or in a school may spread rapidly to epidemic proportions. It is highly important, therefore, to exercise rigid precautions when a case is discovered. These include complete isolation and careful sterilization of diapers, linens and toilet articles. If a case develops in a children's ward of a hospital, the entire ward should be isolated and all the other children carefully examined at frequent intervals. In short, one cannot be too careful in the management of these cases to prevent the spread of this distressing infection.

Until 1933, when Lewis<sup>1</sup> suggested the use of theelin, the treatment of this disease had been notoriously unsatisfactory. Practically all the known germicides and antiseptics had been tried and recommended but the multitude of methods suggested was in itself evidence of the inefficacy of any one. One needs only to recall the depth to which this infection travels to understand the futility of attempting to destroy the organ-

isms by applying germicides to the vaginal mucous membrane. For the purpose of cleanliness, irrigations with antiseptic solutions are useful and should be employed as will be described, but we should not lead ourselves to believe that we are destroying the gonococci in this manner.

The background of the use of ovarian hormone in the treatment of this disease is of interest. In 1928 Edgar Allen<sup>2</sup> had shown that injections of ovarian hormone for twenty-one days into the immature female monkey caused the vaginal epithelium to increase in thickness from 4 to 8 layers in the controls, to 30 or more layers in the treated animals, and furthermore this was associated with the development of a cornified layer and the appearance of many desquamated epithelial cells in the vaginal smears. There was an associated development of the cervical glands which were invaded by leukocytes, and the endometrium was built up at most to a midinterval phase.

It is known that gonorrheal vaginitis in children tends to subside spontaneously at or before puberty, when the vaginal mucous membranes become adult in type and furthermore, that the gonococcus does not invade the adult vaginal mucosa. Reasoning from these facts, Lewis<sup>1</sup> conceived the idea of artificially changing the vaginal mucosa of the child by the use of theelin, thereby rendering it unfavorable to invasion by the gonococcus. Its use appeared to be harmless, since Hartman<sup>3</sup> had shown that a dose sufficient to produce changes in the vaginal epithelium was much below that which might lead to injurious changes and uterine bleeding, and furthermore, Allen<sup>2</sup> had shown that all changes returned to normal in four to six weeks after treatment with ovarian hormone was discontinued. From the present available clinical reports, it would appear that the administration of this hormone to children is without deleterious effects, although it should be used with caution and all possible secondary effects carefully noted.

Lewis reported good results in the treatment of 4 cases of chronic and 4 of acute gonorrheal vaginitis. Seven patients

were apparently cured and free from recurrence while recurrence was noted in only one. Huberman and Israeloff<sup>4</sup> later reported good results in 6 patients following the use of amniotin. In one of their cases the amniotin was administered by mouth and the patient was clinically cured within eight weeks and this was followed by no recurrence. This latter is of particular importance because of the obvious advantage of oral administration in children. Other reports by Nabarro and Signy,<sup>5</sup> Reading,<sup>6</sup> and Brown<sup>7</sup> attest to the efficacy of estrogenic hormone in the treatment of this disease. In all cases, the disease appears to have been cured in a shorter period of time and with lasting results. The appearance of desquamated epithelial cells in the vaginal smear is taken to be the criteria of adequate treatment and associated with this the purulent discharge changes to a thick, dry adult type of leukorrhea. Following cessation of treatment, there is an involution of the vaginal structures.

Let us then outline a satisfactory treatment for the child with gonorrheal vulvovaginitis. The treatment is the same whether it be an acute or a chronic infection, although it has been noted that the chronic case usually clears up more rapidly following treatment with estrogenic hormone.

The patient should be started immediately on estrogenic hormone (such as theelin, amniotin, progynon or menformon) and this should be given daily until negative vaginal smears are obtained. This hormone may be given hypodermically or by mouth. One hundred rat units daily is usually adequate if hypodermic injection is used, while about five times this dose should be used in case of oral administration. From all clinical and experimental observations, it appears that oral administration is entirely effective, and its obvious advantage in children should make it the method of choice. Vaginal smears should be made at frequent intervals, and the effectiveness of the treatment is judged by the appearance of numerous desquamated epithelial cells in the smear.

In addition to this, the vaginal canal should be irrigated carefully each day and for this purpose, one may select from

a number of solutions, although we have found a 1:5000 solution of potassium permanganate quite suitable. A soft rubber catheter introduced into the vagina serves admirably as an instrument for this purpose and usually is less objectionable to the child than a rigid instrument. The solution should be comfortably hot and at least a quart used at each irrigation.

Other measures are seldom necessary in the average case. Should an infection prove unusually obstinate, however, the cause may be a resistant cervicitis which should be treated by cauterization of the cervix with 20 per cent silver nitrate solution or linear cauterization as suggested by Titus and Notes.<sup>8</sup> Another cause may be a proctitis which should be treated by low rectal irrigations followed by the instillation into the rectum of a 4 per cent solution of argyrol or  $\frac{1}{2}$  per cent protargol.

Crossen<sup>9</sup> has reported good results by the use of diathermy which may be employed to good advantage, especially if there is any evidence of pelvic inflammation.

With any form of treatment, however, the possibility of recurrence is to be borne in mind, and all patients should be followed carefully to assure a lasting cure. Reinfection may also occur, so that all possible sources of infection in the child's environment (parents, nursemaids, etc.) must be carefully controlled.

Fortunately, it is rare for any effects of a vulvovaginitis to persist into adult life; therefore, one can give a good prognosis once a cure has been established.

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## TREATMENT OF CHRONIC HYPOGLYCEMIA

E. PERRY McCULLAGH

It is the custom at present to consider cases of chronic hypoglycemia without obvious cause to be instances of hyperinsulinism. This may or may not be warranted, since our present methods do not make it possible to measure with accuracy such factors as the function of the liver, the pituitary or adrenals in this respect.

Some of the common causes of hypoglycemia which must be considered are:

1. **Excess of Insulin.**—This may follow injections of insulin in diabetics or it may be associated with hyperactivity of the insulogenic function and in some cases has been associated with hypertrophy of the islands of Langerhans or with benign or malignant tumors. Hypoglycemia occurs very frequently four or five hours after a large amount of glucose has been taken such as in a glucose tolerance test. In the majority of instances, this is not associated with symptoms and it presumably is the result of stimulation of insulin production. Hypoglycemic reactions occur in some diabetics apart from insulin medication.

2. **Deficient Glycogenesis.**—This may be present following destruction of the liver by poisons, acute yellow atrophy, and extensive destruction by tumors. Probably cirrhosis is a factor in some cases. Hypoglycemia has been shown to be associated with extensive fatty metamorphosis of the liver in late diabetes.<sup>1</sup> It seems probable that functional liver disease may produce the same effect. Muscle wasting may produce hypoglycemia and the mechanism in some instances appears to be on the basis of glycogen deficiency. Starvation, excessive exercise, and occasionally loss of sugar by lactation or in renal glycosuria may be factors.

3. **Endocrine Disorders Affecting Other Glands.**—The influence of the pituitary gland on sugar metabolism is obvious in cases of pituitary tumors and in cases of extensive pituitary damage such as in Simmond's disease. Hypothyroidism is frequently associated with hypoglycemia but in both the above instances the hypoglycemia may be asymptomatic. Disease of the suprarenal glands may produce a similar result and hypoglycemia is an almost constant finding in Addison's disease and has been reported in the presence of adrenal tumor.<sup>2</sup>

4. **Organic Nervous Disease.**—The presence of organic nervous disease must be ruled out. We have seen abnormally low glucose tolerance curves in cases of brain tumor.

No discussion will be made here of the diagnosis of hyperinsulinism and the above groups are cited simply to emphasize the fact that the causes of hypoglycemia are multiple, and that the condition does not always produce symptoms.

The symptoms of the condition are extremely variable. In mild cases the common symptoms are excessive hunger, weakness, tremor, excessive sweating, anxiety and inability to concentrate the thoughts. In more severe cases, mental lapses, grand mal, violent delirium and death have been described.

When the condition is suspected, the chief points in diagnosis are that the symptoms are relieved by food or glucose and can be shown to be associated with blood sugar levels which usually are definitely below 70 mg. per 100 cc.

Many conditions such as psychoneuroses, psychoses, encephalitis, intracranial neoplasm, epilepsy, alcoholic intoxication and coma from various causes must be borne in mind as sources of similar symptoms.

When all these factors are considered, it is obvious that no standard treatment can be applied in all cases, but must be varied in accordance with the cause of the condition. The most satisfactory treatment in most instances is by dietary measures, which may be supplemented in some cases with endocrine therapy or drug therapy and in the more severe instances surgery must be considered.

The dietary principles which we have found most effec-

tive are (1) frequent feedings and (2) the use of high fat, low carbohydrate diets.

It is generally conceded that a high intake of carbohydrate may increase the tolerance to carbohydrate and tend to lower the blood sugar. This is true not only in nondiabetics but in many diabetics as well, and has led to the general use of much higher intake of carbohydrate in diabetics than was formerly used.

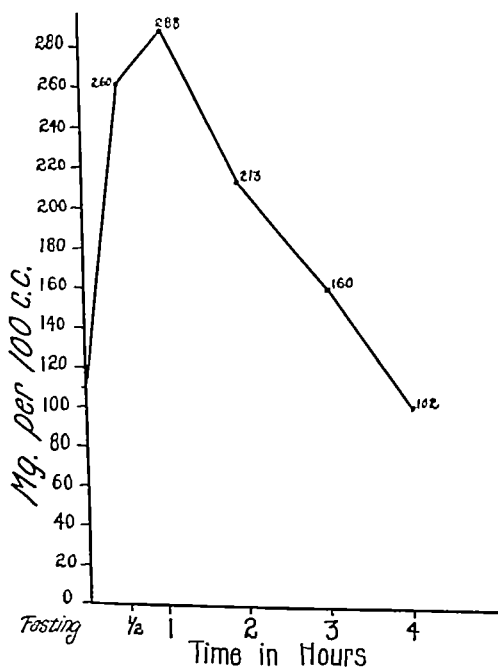


Fig. 191.

The accompanying graphs (Figs. 191–198) show the rather marked effect that may be observed in suitable cases.

The patient was a middle-aged woman who entered the hospital with a history of rather marked alcoholism and numbness and pain in the extremities which was thought to be due to vitamin deficiency, since her food intake had been very low for several weeks.

Figure 191 shows the glucose curve after 100 Gm. of glucose had been taken by mouth.

A tentative diagnosis of diabetes mellitus was made and the patient was placed on a high carbohydrate diet, quickly increasing the intake to 280 Gm. per day. At this time the protein intake was 86 Gm. and the fat intake was 60 Gm.

Twenty days later the glucose tolerance was repeated and the curve is shown in Fig. 192.

It has been recognized for a long time that low carbohydrate, high fat diets may lead to elevation of blood sugar levels. In 1923 the effects of diets in the treatment of epilepsy were reported by Weeks, Renner, Allen and Wishart.<sup>3</sup> These in-

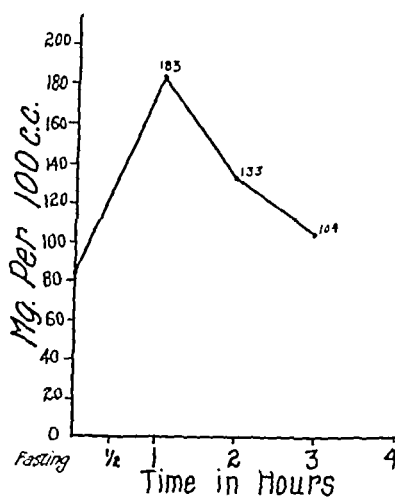


Fig. 192.

investigators placed 6 patients on very high fat, extremely low carbohydrate diets for forty-eight days. In every patient hyperglycemia gradually developed. The highest figure reached was 357 mg. per 100 cc.

The usual explanation of the mechanism is that since the blood sugar rises but little, insulin production is not stimulated. In consequence, the fall in blood sugar levels which would ordinarily take place does not occur. On this basis, Harris<sup>4</sup> suggests the use of daily diets of 90 Gm. carbohydrate, 60 Gm. protein and 180 Gm. of fat in the treatment of hyperinsulinism. This he divides into 7 feedings per day. For

obese patients he suggests the use of a diet containing 90 Gm. carbohydrate, 60 Gm. protein and 60 Gm. of fat, making a total caloric intake of 1140, while in underweight individuals, 90 Gm. carbohydrate, 60 to 75 Gm. protein and 200 to 300 Gm. of fat are used.

Such cases as those reported by Shepardson<sup>5</sup> illustrate the value of this treatment. In one case of hypoglycemia treated with a high fat diet ranging from 100 Gm. carbohydrate, 80 to 90 Gm. protein and 200 to 280 Gm. fat, the blood sugar levels four and one-half and five hours after meals rose from 66 and 60 mg. per 100 cc. preceding treatment to 98 mg. per 100 cc. five and one-half hours P. c. one week later, and more than three weeks after treatment was begun, levels rang-

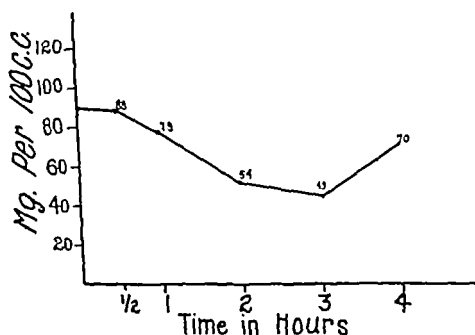


Fig. 193.

ing from 97 to 117 mg. per 100 cc. five hours P. c. were found. These changes were associated with marked clinical benefit. In another case, the blood sugars rose on a high fat diet from 58 mg. per 100 cc. before treatment to 81 mg. per 100 cc. one month after treatment was instituted.

The type of result which may be observed is illustrated by the following case: a white man, twenty-nine years of age, in 1932 complained that for nine years he had had frequent spells of weakness, nervousness and perspiring of the entire body. At times this was accompanied by a tendency to stutter and to be confused mentally. He had not associated his symptoms with meals, as he felt very fatigued most of the time. He had been forced to stop work for several months

because of poor endurance, severe headaches and marked insomnia. On June 2, 1932, his glucose tolerance was measured using 100 Gm. of glucose orally. The results are shown in Fig. 193.

A diagnosis of chronic hypoglycemia was made and a diet was prescribed which contained approximately 105 Gm. of carbohydrate, 75 Gm. of protein and 250 Gm. of fat with food between meals and at bedtime. Within two weeks the symptoms had disappeared entirely. Headaches which were previously frequent, severe and sustained for many days at a time have not occurred more than about once a year since treatment. A severe headache was precipitated by a glucose tolerance test which was done January 8, 1935 (Fig. 194).

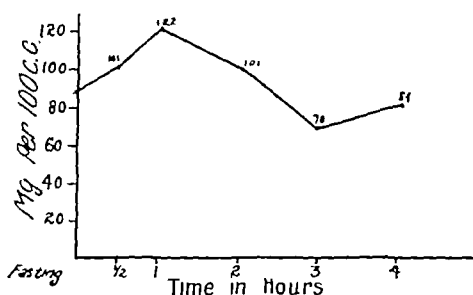


Fig. 194.

While the fasting blood glucose level is not altered, there is a distinct change in the tolerance.

A second case illustrating this point may be cited. A white woman, forty-one years of age, was referred to Dr. George Crile by Dr. W. E. Blanchard with a diagnosis of chronic cholecystitis and hyperinsulinism with possible pancreatic tumor. It required a very careful history to elicit the fact that the chronic fatigue was aggravated by spells of weakness and sweating. Neither were the attacks always relieved by eating. Cholecystogram revealed a nonfunctioning gallbladder with stones. On August 7, 1935, glucose tolerance test was given, using 100 Gm. of glucose orally. The blood sugar levels are shown in Fig. 195.

A diet was instituted which contained 100 Gm. carbohydrate, 70 Gm. protein, and 150 Gm. of fat, with feedings between meals and at bedtime. One month following our first

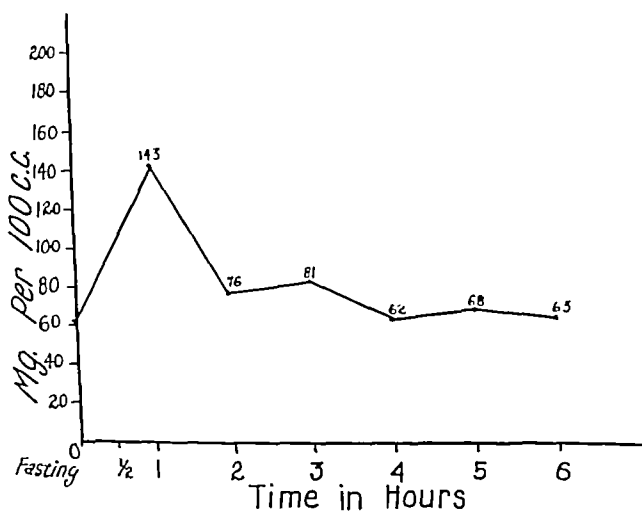


Fig. 195.

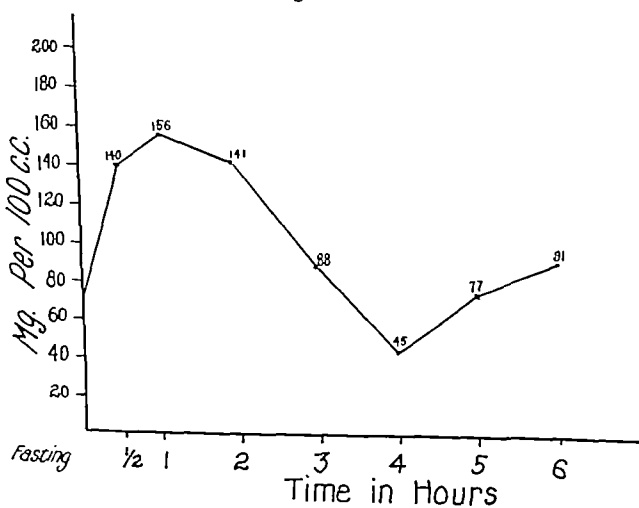


Fig. 196.

examination, the glucose tolerance test was repeated and the results are shown in Fig. 196. At about the fourth hour the patient had an attack of marked weakness, trembling and



sweating which coincided exactly in her mind with her previous attacks.

Cholecystectomy was performed on September 9, 1935, and an uneventful convalescence followed. The diet was continued. No hypoglycemic reactions occurred and general strength has continued to increase.

A glucose tolerance test on November 8, 1935, showed the results seen in Fig. 197. During this test 0.63 Gm. of sugar appeared in the urine. Because of the very marked effect on carbohydrate tolerance and because of the tendency to glyco-

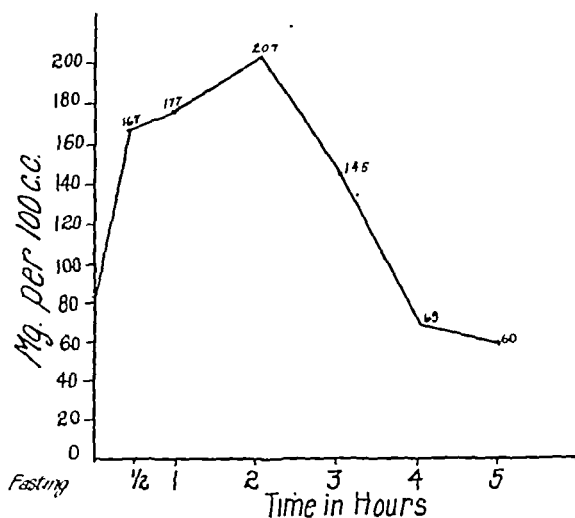


Fig. 197.

suria, the question was raised as to whether or not such a response was due entirely to the effect of the diet or whether, as in some cases, other factors were at work which were carrying this patient toward diabetes.

The problem was explained to the patient and again her cooperation was solicited. On January 4, 1936, a high carbohydrate diet was instituted which contained 275 Gm. carbohydrate, 85 Gm. protein and 70 Gm. fat per day with nourishment between meals and at bedtime. On January 29, 1936, the glucose tolerance was again performed with the result shown in Fig. 198.

It seems to have been thoroughly established in this case that the type of low carbohydrate, high fat diet used allowed the tolerance for glucose to decrease and blood sugar levels to rise, even to diabetic levels. The high carbohydrate diet, on the other hand, was capable of forcing the blood sugar levels downward and increasing glucose tolerance markedly.

It might be added that the diet in this case is accurately weighed under the direct supervision of a skilled dietitian.

If diets in such cases are to be efficient, they must be taught as accurately as diets are taught to a diabetic or they will lose

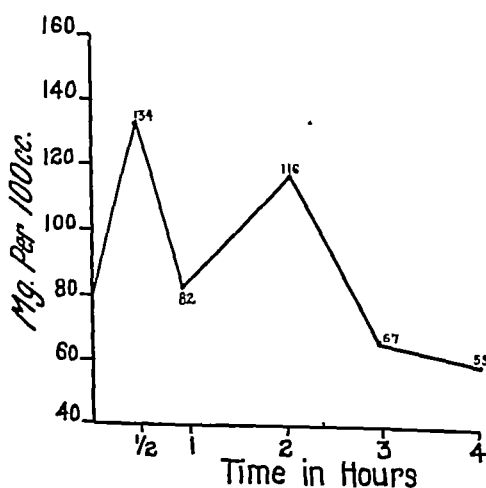


Fig. 198.

their value. Samples of high fat diets, of various caloric value which may be used in the treatment of hypoglycemia, are appended.

For the treatment of an acute attack of hypoglycemia, nothing is as effective as intravenous glucose which may be given in a 25 or 50 per cent solution. This is especially valuable in the case of an unconscious patient. Even in unconsciousness, dry sugar placed in the mouth may be sufficient. The rectal administration of glucose is of little value. If the patient is conscious, orange juice alone or with from 10 to

30 Gm. of glucose or cane sugar is almost always promptly effective. One-half to 1 cc. of 1:1000 solution of epinephrine may be of help. Ephedrine and caffeine are of less value.

Various endocrine products have been suggested for the treatment of hypoglycemia. John<sup>6</sup> describes a method of treatment in which insulin is used to prevent the rise of blood sugar in an attempt to offset in turn the stimulation of the pancreas and the production of excessive amounts of insulin. Although the patients may be relieved by such measures, it has not been shown that there is the marked change in tolerance which may follow the use of high fat, low carbohydrate diets. The value of the method has not as yet been confirmed adequately.

The use of thyroid medication is indicated if the metabolism is low but little effect can be expected from it unless sufficient amounts are given to raise the metabolic rate to heights which are undesirable. Ziskind,<sup>7</sup> for instance, reports no increase in blood sugar levels after giving a patient 34 grains of thyroid per day which was sufficient to raise his basal metabolic rate to +52 per cent.

Very little benefit is obtained from the use of pituitary extracts such as are now available in forms to be given either by mouth or hypodermically, and little or nothing is to be gained by giving adrenal substance orally.  $\alpha$ -Ray radiation of the pancreas has apparently not been given sufficient trial to warrant any comments regarding its value. The diabotogenic hormone of the pituitary gland promises to be of value when it becomes available.

When frequent feedings, diets, and other measures fail to control the symptoms, severe functional hyperinsulinism is to be considered, tumor of the pancreas may be present and surgery is indicated. On the whole, however, operative results have been poor except in those instances where a pancreatic tumor has been removed. It is to be hoped that improvement in surgical technic and removal of larger proportions of the pancreas than has been practiced in the past, will give more complete and consistent relief in severe cases in the future.

## I. LOW CALORIE DIET

Carbohydrate, 60 Gm.; protein, 60 Gm.; fat, 80 Gm. Total calories, 1200.

	Grams.	Household measure.
<i>Breakfast:</i>		
Fruit, 10 per cent. ....	50	$\frac{1}{2}$ serving (see list)
or Tomato juice, 5 per cent. ....	100	
Egg .....		1
Butter. ....	5	$\frac{1}{2}$ square
Whole milk. ....	100	$\frac{1}{2}$ glass
10.00 A. M.:		
Whole milk. ....	100	$\frac{1}{2}$ glass
<i>Luncheon:</i>		
Clear broth. ....		as desired
Meat. ....	60	2 ounces
Cooked vegetable, 5 per cent. ....	100	$\frac{1}{2}$ cup
Butter. ....	10	1 square
Fruit, 10 per cent. ....	50	$\frac{1}{2}$ serving (see list)
3.00 P. M.:		
Whole milk. ....	100	$\frac{1}{2}$ glass
<i>Dinner:</i>		
Meat. ....	90	3 ounces
Cooked vegetable, 5 per cent. ....	100	$\frac{1}{2}$ cup
Raw vegetable, 5 per cent. ....	100	1 cup
Butter. ....	10	1 square
Whole milk. ....	100	$\frac{1}{2}$ glass
Fruit, 10 per cent. ....	50	$\frac{1}{2}$ serving (see list)
9.00 P. M.:		
Whole milk. ....	100	$\frac{1}{2}$ glass
Cream, 20 per cent fat. ....	100	$\frac{1}{2}$ glass

*Sample Menu**Breakfast:*

- $\frac{1}{2}$  glass tomato juice
- 1 coddled egg
- $\frac{1}{2}$  square of butter
- $\frac{1}{2}$  glass whole milk

## 10.00 A. M.:

- $\frac{1}{2}$  glass whole milk

*Luncheon:*

- Beef broth, 1 cup
- 2 ounces assorted cold cuts

$\frac{1}{2}$  cup sliced tomatoes  
 $\frac{1}{2}$  cup cold asparagus  
 1 teaspoonful mayonnaise  
 $\frac{1}{2}$  cup cantaloupe

3.00 P. M.

$\frac{1}{2}$  glass whole milk

*Dinner:*

Consomme  
 3 ounces steak  
 $\frac{1}{2}$  cup brussels sprouts  
 1 cup celery tips  
 1 square butter  
 $\frac{1}{2}$  glass whole milk  
 1 slice pineapple

9.00 P. M.

$\frac{1}{2}$  glass milk  
 $\frac{1}{2}$  glass 20 per cent cream

## II. MEDIUM CALORIC VALUE

Carbohydrate, 90 Gm.; protein, 75 Gm.; fat, 160 Gm. Total calories, 2100.

	Grams.	Household measure.
<i>Breakfast:</i>		
Fruit, 10 per cent. . . . .	100	1 serving (see list)
Egg . . . . .		1
Butter . . . . .	10	1 square
Whole milk . . . . .	100	$\frac{1}{2}$ glass
Cream, 20 per cent. . . . .	100	$\frac{1}{2}$ glass
10.00 A. M.		
Whole milk . . . . .	100	$\frac{1}{2}$ glass
Cream, 20 per cent. . . . .	100	$\frac{1}{2}$ glass
<i>Luncheon:</i>		
Broth . . . . .		as desired
Meat . . . . .	90	3 ounces
Cooked vegetables, 5 per cent. . . . .	100	$\frac{1}{2}$ cup
Butter . . . . .	20	2 squares
Fruit, 10 per cent. . . . .	100	1 serving (see list)
3.00 P. M.		
Whole milk . . . . .	100	$\frac{1}{2}$ glass
Cream, 20 per cent. . . . .	100	$\frac{1}{2}$ glass

*Dinner:*

Broth.....		as desired
Meat.....	90	3 ounces
Cooked vegetable, 5 per cent .....	100	$\frac{1}{2}$ cup
Raw vegetable, 5 per cent .....	100	1 cup
Butter.....	15	1 $\frac{1}{2}$ squares
Whole milk.....	100	$\frac{1}{2}$ glass
Fruit.....	100	1 serving (see list)

## 9.00 P. M.

Whole milk ..	100	$\frac{1}{2}$ glass
Cream, 20 per cent.....	100	$\frac{1}{2}$ glass

*Sample Menu**Breakfast:*

- $\frac{1}{2}$  glass orange juice
- 1 egg—soft-boiled
- 1 square butter
- $\frac{1}{2}$  glass milk
- $\frac{1}{2}$  glass, 20 per cent cream

## 10.00 A. M.

- $\frac{1}{2}$  glass milk
- $\frac{1}{2}$  glass, 20 per cent cream

*Luncheon:*

- Broiled liver, 3 ounces
- $\frac{1}{2}$  cup cooked broccoli
- 2 squares butter
- 1 small baked apple

## 3.00 P. M.

- $\frac{1}{2}$  glass milk
- $\frac{1}{2}$  glass, 20 per cent cream

*Dinner:*

- Broth, 1 cup
- 3 ounces roast lamb
- $\frac{1}{2}$  cup string beans
- 1 cup mixed vegetable salad
- 1 $\frac{1}{2}$  squares butter
- $\frac{1}{2}$  glass milk
- $\frac{1}{2}$  cup unsweetened canned cherries

## 9.00 P. M.

- $\frac{1}{2}$  glass milk
- $\frac{1}{2}$  glass 20 per cent cream

## III. HIGH CALORIE DIET

Carbohydrate, 100 Gm.; protein, 75 Gm.; fat, 250 Gm. Total calories, 3000.

	Grams.	Household measure.
<i>Breakfast:</i>		
Fruit, 10 per cent.....	100	1 serving (see list)
Egg.....		1
Toast.....	15	1 thin slice
Butter.....	30	3 squares
Cream, 20 per cent.....	100	$\frac{1}{2}$ glass
Whole milk.....	100	$\frac{1}{2}$ glass
10.00 A. M.		
Cream, 20 per cent.....	200	1 glass
<i>Luncheon:</i>		
Meat.....	90	3 ounces
Cooked vegetable, 5 per cent.....	100	$\frac{1}{2}$ cup
Butter.....	25	2 $\frac{1}{2}$ squares
Fruit, 10 per cent.....	100	1 serving (see list)
3.00 P. M.		
Cream, 20 per cent.....	200	1 glass
<i>Dinner:</i>		
Broth.....		as desired
Meat.....	120	4 ounces
Cooked vegetable, 5 per cent.....	100	$\frac{1}{2}$ cup
Raw vegetable, 5 per cent.....	100	$\frac{1}{2}$ cup
Butter.....	40	4 squares
Bread.....	15	1 thin slice
Fruit, 10 per cent.....	100	1 serving (see list)
9.00 P. M.		
Cream, 20 per cent.....	200	1 glass

*Sample Menu**Breakfast:*

- $\frac{1}{2}$  glass orange juice
- 1 poached egg
- 1 thin slice toast
- 3 squares butter
- $\frac{1}{2}$  glass whole milk
- $\frac{1}{2}$  glass 20 per cent cream

10.00 A. M.

- 1 glass 20 per cent cream

*Lunch:*

- 3 ounces meat balls
- $\frac{1}{2}$  cup cooked tomatoes
- $2\frac{1}{2}$  squares butter
- 1 medium sized peach

3.00 P. M.

- 1 glass 20 per cent cream

*Dinner:*

- Broth, 1 cup
- 4 ounces roast chicken
- $\frac{1}{2}$  cup spinach
- 1 cup lettuce hearts
- 3 teaspoonfuls mayonnaise
- $2\frac{1}{2}$  squares butter
- 1 thin slice of bread
- $1\frac{1}{2}$  cup strawberries

9.00 P. M.

- 1 glass 20 per cent cream

The 3000 calorie diet above has sufficient fat content as compared to carbohydrates to produce ketosis in some individuals, so that it is advisable to raise the fat content to this level gradually.

Since only 5 per cent vegetables are used, little error will arise from using a standard 8 ounce measuring cup to measure these. The glasses referred to are 6 ounce drinking glasses.

One square of butter is a slice from a quarter pound and will measure approximately  $1\frac{1}{4} \times 1\frac{1}{4} \times \frac{3}{4}$  inches. A thin slice of bread is a piece cut from a standard square loaf and is  $3\frac{1}{2} \times 3\frac{1}{2} \times \frac{1}{4}$  inches.

One serving of fruit selected from any of the following may be substituted for fruit anywhere in the lists given. Unsweetened cooked fruit may be measured the same as uncooked fruit.

A list of 5 per cent vegetables is also appended.

*Each of the following contains 10 grams of carbohydrate and is one serving:*

Apple (raw)	$\frac{1}{2}$ apple, 3 inches in diameter
Applesauce	6 tablespoonfuls
Apricots	2 apricots, $1\frac{1}{4}$ inches in diameter
Cantaloupe	1 cup or $\frac{3}{4}$ of a melon, $4\frac{1}{4}$ inches in diameter
Cherries (sour)	$\frac{1}{2}$ cup
Cherries (sweet)	$\frac{1}{2}$ cup
Cranberries	1 cup
Grapefruit	$\frac{1}{2}$ grapefruit, 4 inches in diameter
Grapefruit juice	$\frac{1}{2}$ glass
Grapes	1 small bunch or 18 grapes
Honeydew melon	$\frac{1}{2}$ cup, cubed



Orange	1 orange (California 150's—Diam. 3") (Florida 176's—Diam. 2½")
Orange juice	½ glass
Peach	1 medium sized
Pear	½ large sized
Pineapple	½ cup diced or 2 slices
Plums	2—1½ inches in diameter
Raspberries	¾ cup
Rhubarb (cooked)	1½ cups
Tangerines	1—3 inches in diameter
Tomato juice	1 glass
Strawberries	1½ cups

*Vegetables, 5 per cent:*

Asparagus	Eggplant	Romaine
Beet greens	Green pepper	Sauerkraut
Broccoli	Kale	Spinach
Brussels sprouts	Kohlrabi	String beans
Cabbage	Leeks	Swiss chard
Cauliflower	Lettuce	Tomatoes
Celery	Mushrooms	Turnip tops
Celery cabbage	Okra	Wax beans
Cucumbers	Parsley	Summer squash
Endive	Radishes	Watercress

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## INDEX TO VOLUME 19

- ABDOMINAL distention in pneumonia, treatment, *July*, 13  
 Hodgkin's disease, *Sept.*, 423-427  
 pain, clinical significance and relief, *Jan.*, 1113-1129  
     in children, *March*, 1603-1615  
     severe, following emotional storm, *Sept.*, 399-402  
 paracentesis in congestive failure, *March*, 1570  
 ptosis, *May*, 1807  
 trauma, psychic effect, *Nov.*, 837-845  
 Abortion, habitual, *Nov.*, 829; *March*, 1450  
     threatened, *March*, 1666, 1667  
 Abscess, Bezold's, *Jan.*, 1045  
     of Bartholin's gland in gonorrhea, *Nov.*, 919  
     of brain, eye symptoms, *Jan.*, 1214  
     of lung, bronchial obstruction in, *Sept.*, 456, 462  
     complicating pneumonia, *July*, 33, 34  
     parapharyngeal, *Jan.*, 1152  
     pelvic, gonorrheal, *Nov.*, 921  
     subperichondrial, *Jan.*, 1051  
     suburethral, gonorrheal, *Nov.*, 922  
 Absorption, gastro-intestinal, clinical factors, *March*, 1685-1693  
 Acetyl- $\beta$ -methylcholine in arterial hypertension, *March*, 1351  
     in paroxysmal tachycardia, *Nov.*, 860  
 Acetylcholine in arterial hypertension, *March*, 1350  
 Achlorhydria in conditions other than pernicious anemia, *July*, 48  
 Achlorhydric anemia, simple, *July*, 69  
 Acidosis, diabetic, in children, prevention, *July*, 279  
 Acrodynia, *Nov.*, 957  
 Acromegaly, *Nov.*, 822-824  
 Adams-Stokes syndrome, emergency treatment, *May*, 1863  
 Addison's disease, diagnosis and treatment, *Sept.*, 383-398  
     emaciation in, treatment, *May*, 1854  
     salt therapy, *Nov.*, 959-965  
 Addisonian anemia. See *Anemia, pernicious.*  
 Adenitis, abdominal, in children, *March*, 1612  
     cervical, in scarlet fever, treatment, *March*, 1395  
 Adenoma of thyroid gland, calcified, *May*, 1761  
     diffuse, *May*, 1718  
     discrete, *May*, 1720  
     hemorrhage into, *May*, 1761  
     malignant, *May*, 1756, 1774  
 Adenosine in arterial hypertension, *March*, 1351  
 Adenylic acid in arterial hypertension, *March*, 1351  
 Adiposogenital dystrophy, *Nov.*, 826-830  
 Adolescent goiter, *May*, 1717, 1718  
 Adrenalin in hay fever and asthma, *March*, 1476  
 Adson-Brown operation for hypertension, *March*, 1359  
 Agranulocytic angina, *July*, 103-122  
 Agranulocytosis in children, *May*, 1973  
 Air embolism in artificial pneumothorax, *Nov.*, 908  
 Albuminuria in hypothyroidism, *May*, 1747  
 Albuminuric retinitis, *Jan.*, 1236  
 Alcohol in production of pellagra, *July*, 60  
     of sprue, *July*, 63  
     injection in glossopharyngeal neuralgia, *Jan.*, 1029  
     in occipital neuralgia, *Jan.*, 1030  
     in superior laryngeal neuralgia, *Jan.*, 1029  
     in trigeminal neuralgia, *Jan.*, 1018-1027  
     intrinsic, for pelvic pain, *Jan.*, 1133  
     paravertebral, for angina pectoris, *March*, 1330  
     use of, in angina pectoris, *Nov.*, 884; *Jan.*, 1104  
 Alcoholic neuritis, *July*, 68; *Nov.*, 951  
 Alcoholism, acute, convulsions in, *July*, 244

- Alkyl nitrates in arterial hypertension, *March*, 1347
- Allergic cleanliness, *March*, 1481
- Allergy, food, and pruritus vulvae, *May*, 1903
- in cyclic vomiting, *May*, 1931-1940
- in children, abdominal pain in, *March*, 1612
- in intestinal toxemia, *May*, 1825
- pollen, *March*, 1467-1492, 1547-1562; *May*, 1915-1930
- Alopecia areata, *Jan.*, 1242; *March*, 1631
- Amenorrhea, *March*, 1453
- Amidopyrine in causation of agranulocytic angina, *July*, 110-118
- Aminophyllin in heart disease, *March*, 1321
- Ammonia dermatitis in infants, *May*, 1882
- Amputation of cervix in gonorrhea, *Nov.*, 917
- Amyl nitrite in angina pectoris, *Jan.*, 1099
- Amyloid nephrosis, proteosuria in, *July*, 177-184
- Amyloidosis, Congo red test, *July*, 179
- Androcin, *May*, 1949
- Anemia, achlorhydric, simple, *July*, 69
- addisonian. See *Anemia, pernicious*.
- after gastrectomy and gastro-enterostomy, *July*, 67
- deficiency, *July*, 37
- Dibothriocephalus latus, *July*, 64, 65
- hypochromic, idiopathic, *July*, 69, 72
- in children, *May*, 1968-1971
- in inoperable cancer, treatment, *July*, 201
- in rheumatoid arthritis, treatment, *March*, 1372
- intestinal malabsorption and, *March*, 1689
- macrocytic, *July*, 38
- tropical, *July*, 66
- with mechanical defects in gastrointestinal tract, *July*, 67
- microcytic, *July*, 59, 69
- nutritional, *July*, 37-77
- of pregnancy, *July*, 39, 65
- pernicious, *July*, 37-59; *March*, 1496
- as deficiency disease, *Sept.*, 469
- comparison with pernicious leukopenia, *July*, 105
- neurological manifestations and their treatment, *July*, 79-89
- secondary, classification, *July*, 91
- treatment, *July*, 91-101
- transfusions in, *May*, 1978
- Angina, agranulocytic, *July*, 103-122
- pectoris in gallbladder disease, *Nov.*, 654
- pain simulating, *Jan.*, 1077
- treatment, *Nov.*, 880-887; *Jan.*, 1085-1111; *March*, 1321, 1330, 1333
- with hyperthyroidism, *May*, 1726
- Anorexia in inoperable cancer, treatment, *July*, 197
- Antitoxin, diphtheria, therapeutic use, *March*, 1401
- meningococcus, *March*, 1423
- scarlet fever, *Jan.*, 1285; *March*, 1389
- staphylococcus, *March*, 1426
- tetanus, *Jan.*, 1284
- Antophysin, *Nov.*, 818
- Antuitrin, *Nov.*, 818
- Aorta and its larger branches, embolism and thrombosis of, *July*, 159-170
- Aortic regurgitation, murmurs of, *March*, 1513
- stenosis, calcareous, *Sept.*, 487-497
- Appendicitis, acute, atypical, diagnosis, *July*, 185-194
- in children, *March*, 1606
- in scarlet fever, treatment, *March*, 1398
- pain in, *Jan.*, 1122, 1124
- Apple diet in diarrhea of infants and children, *July*, 301-305
- Arm, epitheliomas of, simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610
- Arrhythmia in gallbladder disease, *Nov.*, 658
- in hyperthyroidism, *May*, 1725
- Arsenic in treatment of secondary anemias, *July*, 99
- Arsenical neuritis, *Nov.*, 955
- Arterial hypertension, treatment, *July*, 133-149; *March*, 1343-1365
- hypotension, *Nov.*, 865-871
- Arteriosclerosis associated with hypertension, *July*, 139
- eye symptoms, *Jan.*, 1209
- Arteriosclerotic retinitis, *Jan.*, 1210
- Arteriovenous fistula, congenital, *Sept.*, 525-533
- Arthritis, acute, convalescence from, management, *March*, 1374
- chronic infectious, fever therapy in, *Sept.*, 590
- inactivation by jaundice, *Sept.*, 573-583
- relief by cholecystostomy and cholecystectomy, *Nov.*, 697
- classification, *May*, 1837, 1838
- dietary treatment, *May*, 1837-1847

- Arthritis, gonorrheal, fever therapy, *Sept.*, 551-559, 589; *March*, 1369  
treatment, *March*, 1368-1370  
hypertrophic, low back pain in, at night, *May*, 1800  
menopausal, *July*, 218  
of feet, pain in, *Jan.*, 1071  
postoperative, acute, identification of, *Sept.*, 560-566  
prevention and treatment, *Sept.*, 566-573  
rheumatoid, treatment, *March*, 1370-1375  
with hyperthyroidism, management, *May*, 1729  
Arthrodesis for sciatic pain, *Jan.*, 1038  
Aschheim-Zondek test, *March*, 1452  
Ascorbic acid, *Sept.*, 482  
Asthenia, neurocirculatory, *March*, 1534-1545  
masking hyperthyroidism, *May*, 1739  
Asthma, cardiac, emergency treatment, *May*, 1861  
diagnosis and treatment, *March*, 1467-1492; *May*, 1915  
fever therapy, *Sept.*, 591  
simulating tracheal and bronchial obstruction, *Sept.*, 453  
Atelectasis, massive, *Sept.*, 457  
Aural vertigo, *March*, 1619  
Auricle of ear, pain in, relief, *Jan.*, 1050-1054  
Auricular fibrillation, *Sept.*, 511-515  
quinidine therapy, *March*, 1325  
with hyperthyroidism, *May*, 1725  
Austin-Flint murmur, *March*, 1515  
Autohemotherapy in pruritus, *Nov.*, 982  
Auto-intoxication, intestinal, *May*, 1819  
Autovaccination, *Jan.*, 1280  
  
BACILLUS diphtheriae, rapid culture method, *Nov.*, 736  
Backache, relief of, *Jan.*, 1033-1038  
Barbiturates as soporifics, *March*, 1600  
Bartholin's gland, gonorrheal abscess, *Nov.*, 919  
Basedow's disease, eye symptoms, *Jan.*, 1204  
Basophilism, pituitary, *Nov.*, 831  
Beard, ringworm of, *March*, 1638  
Bed-wetting, *July*, 287  
Beri-beri, *July*, 68  
in gastro-intestinal disease or abnormality, *Sept.*, 468, 469  
vitamin deficiency in, *Sept.*, 481  
Bezold's abscess, *Jan.*, 1045  
Bile, laboratory study, *Nov.*, 680-684  
Bile pigment in secondary anemias, *July*, 100  
Biliary calculi. See *Cholelithiasis*.  
colic, *Nov.*, 642; *Jan.*, 1118, 1124  
disease following cholecystectomy for stones, *Nov.*, 689  
drainage, nonsurgical, *Nov.*, 677-688  
dyskinesia, *Nov.*, 669, 673  
Biliousness, *May*, 1819  
Biopsy, endometrial, *March*, 1440  
Birth injuries, cerebral, convulsions due to, *July*, 249, 254  
corrective motor education in, *Nov.*, 807-815  
psychopathic personality and, *May*, 1991  
Bismuth subnitrate in arterial hypertension, *March*, 1348  
Bites, insect, skin eruptions from, *May*, 1882  
Black dot of scalp, *Jan.*, 1248  
tongue, *July*, 59  
Bladder neck masses, gonorrheal, *Nov.*, 924  
Blastomycosis of skin, *March*, 1646  
cutaneous tuberculosis simulating, *Sept.*, 613, 617  
Blood, cholesterol determinations, *Jan.*, 1167  
clotting function, diets to increase and decrease, *Nov.*, 989-999  
dyscrasia, atypical, jaundice arising from, *Sept.*, 545-550  
in children, diagnosis, *May*, 1967-1975  
in relation to bone marrow failure, *March*, 1525  
typing and matching, *May*, 1982  
Bone, giant-cell tumor, roentgen treatment, *Sept.*, 601  
marrow failure, sequence of events in, clinical importance, *March*, 1525-1531  
Brain, abscess, eye symptoms, *Jan.*, 1214  
defects, congenital, convulsions due to, *July*, 251, 254  
tumors, eye symptoms, *Jan.*, 1217  
gastro-intestinal manifestations, *Jan.*, 1260  
headache in, *Jan.*, 1203  
pain about oral cavity in, *Jan.*, 1065  
Breast conditions, treatment, *March*, 1451  
Breath, uremic, *July*, 237  
Brodie's serum in poliomyelitis prophylaxis, *Nov.*, 742  
Bronchiectasis, abdominal pain in, *Jan.*, 1116  
treatment, *Jan.*, 1171

- Bronchopneumonia, tuberculous, in children, *Nov.*, 717, 718
- Bronchus, obstruction of, clinical and bronchoscopic findings, *Sept.*, 453-462
- Browntail moth dermatitis, *May*, 1883
- Burning tongue, *Jan.*, 1065
- Burns, death from, causes, *May*, 1941
- permanent disability from, *May*, 1942
- treatment, *May*, 1941-1947
- CALCAREOUS aortic stenosis, *Sept.*, 487-497
- Calcium bilirubin masses in bile, *Nov.*, 681
- Calculus, biliary. See *Cholelithiasis*.
- Carbon monoxide polyneuritis, *Nov.*, 958
- Carcinoma, inoperable, treatment, *July*, 195-204
- multiple, complicating chronic ulcerative colitis, *Sept.*, 408-410
- of bronchus causing obstruction, *Sept.*, 455
- of cervical stump after hysterectomy, *Sept.*, 352
- of cervix, diagnosis, *March*, 1443
- incidence, *Sept.*, 350
- pain in, relief, *Jan.*, 1133
- of colon, cooperative management, *Sept.*, 619, 621, 625
- diagnosis, *May*, 1831-1835
- of kidney, roentgen treatment, *Sept.*, 601
- of lungs, bronchial obstruction in, *Sept.*, 456
- of skin, roentgen treatment, *Sept.*, 599
- of small intestine, *Sept.*, 366
- of thyroid gland, *May*, 1721, 1757, 1776, 1777
- roentgen treatment, *Sept.*, 600
- roentgen therapy, *Sept.*, 598-603
- Carcinoma-sarcoma of thyroid gland, *May*, 1757, 1777
- Cardiac asthma, emergency treatment, *May*, 1861
- neurosis, *March*, 1533
- Cardiospasm in gallbladder disease, *Nov.*, 653
- Carotene, *Sept.*, 479
- Carotid sinus dizziness and syncope, *March*, 1624
- Caruncle, urethral, *Nov.*, 923
- Cataract, diabetic, *Jan.*, 1232
- Catarrhal jaundice, biliary drainage in, therapeutic value, *Nov.*, 685
- Cauterization of cervix for cervicitis, *Sept.*, 354
- Cauterization of cervix in gonorrhea, *Nov.*, 915, 918
- Cerebral accidents, coma of, treatment, *Jan.*, 1270
- birth injuries, convulsions due to, *July*, 249, 254
- corrective motor education in, *Nov.*, 807-815
- Cerumen, impacted, *Jan.*, 1052
- Cervical adenitis in scarlet fever, treatment, *March*, 1395
- stump, carcinoma of, following hysterectomy, *Sept.*, 352
- Cervicitis, *Sept.*, 349
- cautery treatment, *Sept.*, 354; *Nov.*, 915, 918
- Elliott heat treatment, *Sept.*, 353
- pruritus vulvae from, *May*, 1899
- Cervix uteri, amputation of, in gonorrhea, *Nov.*, 917
- carcinoma of, diagnosis, *March*, 1443
- pain in, relief, *Jan.*, 1133
- erosion, congenital, *March*, 1441
- gonorrhea of, treatment in nulliparous, *Nov.*, 918
- in parous, *Nov.*, 914
- lesions of, *Sept.*, 347-357
- Cevitamic acid, *Sept.*, 482
- Chickenpox, immunization, *Jan.*, 1290
- Chigger bites, *May*, 1883, 1884
- Children, diseases of, symposium on, *Nov.*, 701
- Chloral as soporific, *March*, 1599
- Choked disk in brain abscess, *Jan.*, 1215
- in brain tumor, *Jan.*, 1217
- Cholangitis, *Nov.*, 665
- biliary drainage in, therapeutic value, *Nov.*, 687
- Cholecystectomy for stones, biliary disease following, *Nov.*, 689
- relief of chronic arthritis by, *Nov.*, 697
- Cholecystitis, chronic, diagnosis, *Nov.*, 641-648
- lenta, *Nov.*, 665
- Cholecystography, *Nov.*, 644
- Cholecystopathica spastica, *Nov.*, 670
- Cholecystostomy, relief of chronic arthritis by, *Nov.*, 697
- Cholelithiasis, cholecystectomy for, biliary disease following, management, *Nov.*, 689
- diagnosis, *Nov.*, 641-648
- nocturnal pain in, simulating indigestion, *May*, 1801
- Cholesterin crystals in bile, *Nov.*, 681
- Cholesterol in blood, determinations, *Jan.*, 1167

- Chordotomy for pelvic pain, *Jan.*, 1140
- Chorea in children, fever therapy, *Sept.*, 591; *Nov.*, 771-784
- Choreo-athetosis, *Nov.*, 808, 809
- Chvostek's sign in tetany, *July*, 242, 255
- Cinchophen in acute postoperative gout, *Sept.*, 570
- Citrate method of blood transfusion, *May*, 1981
- Climacteric. See *Menopause*.
- Clotting function of blood, diets to influence, *Nov.*, 989-999
- Cold test in hypertension, *Sept.*, 518
- Colds, common, *March*, 1499-1504
- in infants and children, *Nov.*, 745-750
- Colic, biliary, *Nov.*, 642; *Jan.*, 1118, 1124
- in infants, *March*, 1609
- renal, *Jan.*, 1119, 1124; *May*, 1804
- Colitis in children, *March*, 1608
- mucous, *Jan.*, 1123, 1128
- ulcerative, chronic, management, *Sept.*, 403-407
- two carcinomas complicating, *Sept.*, 408-410
- idiopathic, in children, *March*, 1673-1683
- regional, *Sept.*, 411-422
- Colon, carcinoma of, cooperative management, *Sept.*, 619, 621, 625
- diagnosis, *May*, 1831-1835
- disturbances in gallbladder disease, *Nov.*, 662, 663
- irritable, pain in, *Jan.*, 1123, 1127
- spastic, in children, *March*, 1608
- intestinal toxemia and, *May*, 1824
- nocturnal pain in, *May*, 1799, 1803
- Coloptosis, *May*, 1808
- Colposcopy, *March*, 1443
- Coma, diabetic. See *Diabetic coma*.
- treatment, *Jan.*, 1265-1271
- Communicable diseases, recent developments, *Nov.*, 731-744; *Jan.*, 1277-1290
- Complement fixation test in tuberculosis in children, *Nov.*, 724
- Congestive heart failure, management, *March*, 1563-1570
- in emergencies, *May*, 1857
- Congo red test in amyloidosis, *July*, 179
- Conization in gonorrhea of cervix, *Nov.*, 914
- Constipation in pregnancy, *March*, 1664
- in splanchnoptosis, treatment, *May*, 1812
- Constitutional psychopathic personalities, *May*, 1985-1997
- Contact dermatitis, *May*, 1884-1890
- Contractures from burns, *May*, 1942
- Convalescent serum in measles, *Jan.*, 1288
- in poliomyelitis, *Jan.*, 1290
- in scarlet fever, *March*, 1393
- Convulsions, *July*, 233-246
- epileptic, *July*, 259-264; *March*, 1583-1595
- epileptiform, *July*, 260
- in children, diagnosis and treatment, *July*, 247-265
- jacksonian, *July*, 260
- Copper in treatment of secondary anemias, *July*, 99
- Corns, *Jan.*, 1072
- Coronary disease, pain simulating, *Jan.*, 1077-1083
- occlusion, abdominal pain in, *Jan.*, 1116
- acute, *Sept.*, 499-510
- emergency treatment, *May*, 1860
- seasonal incidence in Philadelphia, *July*, 151-157
- nocturnal pain in, simulating indigestion, *May*, 1802
- thrombosis, angina pectoris and, differentiation, *Jan.*, 1085
- treatment, *Nov.*, 873-880, 887
- Cretinism, *May*, 1717
- Cryptococcosis epidermica, *March*, 1640
- Cucurbititrin in arterial hypertension, *March*, 1352
- Culture medium, Löwenstein's, in tuberculosis, *Nov.*, 722
- Cutaneous. See *Skin*.
- Cystitis, *May*, 1959-1965
- pruritus vulvae from, *May*, 1899
- Cysts, nabothian, *Sept.*, 349
- tubal, in female gonorrhea, *Nov.*, 920
- DALRYMPLE's sign, *Jan.*, 1208
- Deficiency anemias, *July*, 37
- diseases, intestinal absorption in, *March*, 1688
- methods of production, *Sept.*, 468
- occurrence of, *Sept.*, 466, 474
- pruritus vulvae in, *May*, 1902
- Dehydration in inoperable cancer, treatment, *July*, 202
- Delirium in pneumonia, treatment, *July*, 14
- Denervation of kidney for hypertension, *March*, 1359
- of suprarenal glands for hypertension, *March*, 1358

- Dental field, pain in, *Jan.*, 1057-1066  
 Dermatitis, ammonia, in infants, *May*, 1882  
   browntail moth, *May*, 1883  
   contact, *May*, 1884-1890  
     of vulva, *May*, 1898  
   ivy, *May*, 1885  
   Jacquet's, *May*, 1881  
   ragweed, *May*, 1889  
   solare, *May*, 1876, 1878  
   venenata, *May*, 1884-1890  
 Dermatomycosis, *March*, 1641  
 Dermatopolyneuritis, *Nov.*, 957  
 Dermatoses, light sensitive, *May*, 1877  
   pruritus of, *Nov.*, 979  
   summer, *May*, 1875-1892  
 Deryl-Hart apparatus, *July*, 31  
 Desensitization in hay fever and asthma, *March*, 1483, 1555; *May*, 1922  
 Diabetes, abdominal pain in, *March*, 1613  
   emaciation in, treatment, *May*, 1854  
   eye symptoms, *Jan.*, 1231  
   in children, insulin in, *Nov.*, 791-805  
   management, *July*, 273-286  
   masking hyperthyroidism, *May*, 1741  
   pruritus vulvae in, *May*, 1902  
   with hyperthyroidism, management, *May*, 1728  
 Diabetic coma in children, treatment, *Nov.*, 800  
   treatment, *Jan.*, 1268  
   polyneuritis, *Nov.*, 956  
 Diagnostic methods, new, in gynecology, *March*, 1439  
 Diaphragmatic hernia, anginal pain in, *Jan.*, 1083  
 pleurisy, abdominal pain in, *Jan.*, 1115  
 Diarrhea in hyperthyroidism, *May*, 1737  
   of infants and children, apple diet in, *July*, 301-305  
 Diastolic murmurs, *March*, 1513  
 Diathermy in gonorrhea of cervix, *Nov.*, 914  
 Diathesis, exudative, *July*, 326  
 Dibothriocephalus latus anemia, *July*, 64, 65  
 Dick test, *Jan.*, 1285  
 Diet, apple, in diarrhea of infants and children, *July*, 301-305  
   "bleeding" and "clotting," *Nov.*, 989-999  
   diabetic, in children, *July*, 274  
   elimination, in allergy, *March*, 1482, 1490  
   in pregnancy, *March*, 1663, 1668  
   Karell, *July*, 174  
 Diet, ketogenic, in epilepsy, *July*, 263  
 Dietary treatment of angina pectoris, *Jan.*, 1097  
   of arthritis, *May*, 1837-1847  
   of congestive heart failure, *March*, 1564  
   of coronary thrombosis, *Nov.*, 876, 887  
   of gout, *May*, 1839  
   of hypertension, *July*, 144; *March*, 1353  
   of hypoglycemia, *May*, 2007, 2015  
   of inoperable cancer, *July*, 197  
   of intestinal toxemia, *May*, 1827  
   of nephritis with vascular and cardiac complications, *July*, 175  
   of pneumonia, *July*, 15, 17  
   of rheumatoid arthritis, *March*, 1371; *May*, 1841  
   of secondary anemias, *July*, 97  
   of splachnoptosis, *May*, 1810  
   recent advances, *March*, 1493-1498  
 Digitalis in congestive heart failure, *March*, 1566; *May*, 1858  
   in nephritis with vascular and cardiac complications, *July*, 174  
 Digitalization in pneumonia, *July*, 14  
 Diphtheria antitoxin, therapeutic use, *March*, 1401  
   bacillus, rapid culture method, *Nov.*, 736  
   Schick test, *Jan.*, 1282  
   toxoid for immunization, *Nov.*, 736; *Jan.*, 1281  
   treatment, *March*, 1401-1406  
   with heart involvement, *Nov.*, 737  
 Diphtheritic polyneuritis, *Nov.*, 955  
 Diuretics in congestive heart failure, *March*, 1568  
   in nephritis with vascular and cardiac complications, *July*, 174  
 Diverticula, Meckel's, *Sept.*, 372, 373  
   of small intestine, *Sept.*, 372  
 Diverticulitis, *Sept.*, 374  
   perforation in, management, *Sept.*, 407  
 Dizziness, significance and treatment, *March*, 1617, 1621-1626  
 Drugs, convulsant, poisoning in children by, *July*, 256  
   in causation of pernicious leukopenia, *July*, 110-118  
   poisoning by, treatment, *Jan.*, 1268  
 Ductus arteriosus, patent, *March*, 1517  
 Duodenal feeding, *May*, 1852  
 Duroziez's sign, *March*, 1513  
 Dwarfism, pituitary, *Nov.*, 825, 826  
 Dysinsulinism, *July*, 233

- Dyskinesia, biliary, *Nov.*, 669, 673  
 Dysmenorrhea, *Jan.*, 1132; *March*, 1456  
 Dyspareunia, *July*, 267, 268  
 Dyspepsia in gallbladder disease, *Nov.*, 642  
 Dystrophy, adiposogenital, *Nov.*, 826-830  
  
 EAR drops, *Jan.*, 1042  
     drum, blue, *Jan.*, 1048  
     paracentesis of, *Jan.*, 1042  
     rupture of, traumatic, *Jan.*, 1054  
     foreign bodies in, pain due to, *Jan.*, 1052  
 Earache, reflex, *Jan.*, 1054  
     treatment, *Jan.*, 1039-1055  
 Eclampsia, threatened, *March*, 1669, 1670  
 Eclamptic uremia, acute, *July*, 236, 238  
 Ectropion of cervix, *Sept.*, 349  
 Eczema, contact, *July*, 319-324  
     in infancy and childhood, *July*, 325-331  
     mycoticum, *March*, 1641  
     of ear, *Jan.*, 1050  
 Edema, stasis, in thrombophlebitis, *Sept.*, 542  
     in varicose veins, *Sept.*, 538  
 Elimination diet in hay fever and asthma, *March*, 1482, 1490  
 Elliott heat treatment of cervicitis, *Sept.*, 353  
 Emaciation, treatment, *May*, 1849-1855  
 Embolectomy, *July*, 168  
 Embolism, air, in artificial pneumothorax, *Nov.*, 908  
     of aorta and its larger branches, *July*, 159-170  
     pulmonary, simulating coronary disease, *Jan.*, 1079  
 Embryoma of testis, *Sept.*, 599  
 Emotional factors in epilepsy, *March*, 1591, 1594  
     storm, severe abdominal pains following, *Sept.*, 399-402  
 Emotions and intestinal toxemia, *May*, 1823  
 Empyema complicating pneumonia, surgical management, *July*, 30-33  
     in scarlet fever, treatment, *March*, 1398  
 Encephalitis, epidemic, eye symptoms, *Jan.*, 1228  
     postvaccinal, *Jan.*, 1280  
 Encephalopathy, hypertensive, *July*, 238  
  
 Endocarditis in scarlet fever, treatment, *March*, 1397  
 Endocrine imbalance, psychopathic personality and, *May*, 1993  
     therapy. See *Hormone therapy*.  
 Endometrial biopsy, *March*, 1440  
 Endometritis, pruritus vulvae from, *May*, 1899  
 Enterocolitis, ulcerative, regional, *Sept.*, 411-422  
 Enteroptosis, *May*, 1807, 1809  
 Enuresis in childhood, causes and treatment, *July*, 287-294  
 Ephedrine in hay fever and asthma, *March*, 1478  
 Epidermophytide, *March*, 1644  
 Epidermophytosis, *March*, 1641  
     of vulva, *May*, 1896  
 Epilepsy, *July*, 259-264; *March*, 1583-1595  
     Epileptiform convulsions, *July*, 260  
 Epiphyses, separation of, *Nov.*, 830  
 Epitheliomas of arm simulating endothelioma, sarcoma and sporotrichosis, *Sept.*, 605-610  
     of ear, *Jan.*, 1054  
 Epituberculosis, roentgen findings, *Nov.*, 715  
 Erb's sign in tetany, *July*, 255  
 Erosio interdigitalis, *March*, 1644  
 Erosion of cervix, *Sept.*, 349  
     cautery treatment, *Sept.*, 354  
     congenital, *March*, 1441  
 Erysipelas of auricle, *Jan.*, 1051  
 Erythema solare, *May*, 1876, 1878  
 Erythematous lupus, visceral lesions of, *July*, 333-346  
 Erythrasma, *March*, 1649  
 Erythredema polyneuritis, *Nov.*, 957  
 Estrin, *March*, 1462  
     in amenorrhea, *March*, 1454  
     in dysmenorrhea, *March*, 1457  
     in gonorrheal vulvovaginitis, *May*, 2001  
     in menopause, *July*, 220-224; *March*, 1462  
     in urine, test, *March*, 1440  
 Ethyl iodide inhalations in epidermophytosis, *March*, 1643  
     in tinea, *March*, 1637  
 Eustachian tube, edema of, in hypothyroidism, *May*, 1745  
 Evaporated milk for infants, *Nov.*, 787  
 Eversion of cervix, *Sept.*, 349  
 Ewing's tumor, roentgen therapy, *Sept.*, 602  
 Exophthalmic goiter, eye symptoms, *Jan.*, 1204  
 Extremities, increased length, in arteriovenous fistula, *Sept.*, 526, 528  
     venous diseases, *Sept.*, 535-543



- Exudative diathesis, *July*, 326  
 Eyegrounds, examination, *Jan.*, 1198  
 Eyes, examination, *Jan.*, 1189  
   in acute disseminated lupus erythematosus, *July*, 337  
   symptoms, diagnostic value in  
     in general disease, *Jan.*, 1187-1239  
     in hyperthyroidism, *May*, 1736  
 Eyestrain, headaches due to, *Jan.*, 1202
- FACIAL neuralgia, relief of, *Jan.*, 1017-1028  
 Fainting attacks, *March*, 1622  
 Favus of scalp, *Jan.*, 1249; *March*, 1636  
 Febrile diseases in infants, convulsions due to, *July*, 252  
 Feeding, infant, difficult cases, *Nov.*, 785-789  
 Feet, painful, relief of, *Jan.*, 1067-1075  
 Ferments, pancreatic, *Nov.*, 683  
 Ferry's meningococcus antitoxin, *March*, 1423  
 Fever in acute appendicitis, *July*, 193  
   therapy, *Sept.*, 585-595  
     in chorea in children, *Sept.*, 591; *Nov.*, 771-784  
     in gonococcal arthritis, *Sept.*, 551-559, 589; *March*, 1369  
     in rheumatoid arthritis, *March*, 1372  
 Fibrositis, chronic, inactivation by jaundice, *Sept.*, 573-583  
 Fistula, arteriovenous, congenital, *Sept.*, 525  
   gastrojejuno-colic, anemia with, *July* 67  
     of small intestine, *Sept.*, 377  
 Fits, *March*, 1583-1595  
 Flush, menopausal, *July*, 215  
 Foci of infection, removal in arthritis, *March*, 1371  
 Follutein, *Nov.*, 818  
 Food allergy in mild and severe cyclic vomiting, *May*, 1931-1940  
   pruritus vulvae and, *May*, 1903  
 Foods, vitamin content, advisability of increasing, *Sept.*, 472  
 Foot, march, *Jan.*, 1075  
   strain, *Jan.*, 1073  
 Foreign bodies in bronchus causing obstruction, *Sept.*, 457  
   in ear, pain due to, *Jan.*, 1052  
 Fractures of ribs, pain in, simulating coronary disease, *Jan.*, 1081  
   of skull, eye symptoms, *Jan.*, 1238  
 Freckles, *May*, 1876  
 Friction rubs, pericardial, *March*, 1519  
 Friedman test, *March*, 1452  
 Frigidity in female, *March*, 1448  
 Fröhlich's syndrome, *Nov.*, 826-830  
 Frostbite of ear, *Jan.*, 1053  
 Fundus, eye, examination, *Jan.*, 1201  
 Fungi in external ear, *Jan.*, 1050  
 Fungus diseases of skin, *March*, 1633  
   infections of vulva, *May*, 1896, 1907  
 Furunculosis of ear, *Jan.*, 1049
- GAENSLER'S sign in sacro-iliac lesions, *Jan.*, 1036  
 Galactose tolerance test, *Jan.*, 1167  
 Gallbladder disease, biliary drainage in, diagnostic, *Nov.*, 679  
   therapeutic value, *Nov.*, 687  
   diagnosis, *Nov.*, 641-648  
   metabolic disturbances in, *Nov.*, 664  
   pancreatic disease associated with, *Nov.*, 664  
   symposium on, *Nov.*, 639  
   symptoms, atypical, *Nov.*, 649-675  
   dyskinesia, *Nov.*, 669, 673  
   functional disturbances, *Nov.*, 666  
     treatment, *Nov.*, 672  
   stasis, *Nov.*, 669  
   vertigo, *Nov.*, 653  
 Gallstones. See *Cholelithiasis*.  
 Gas pains, postoperative, *Jan.*, 1125  
 Gasserian ganglion, sensory root avulsion for trigeminal neuralgia, *Jan.*, 1028  
 Gastrectomy, anemia following, *July*, 67  
 Gastric juice in relation to pernicious anemia, *July*, 41  
   lavage for diagnosis of tuberculosis, *Nov.*, 721  
   resection for peptic ulcer, recurrences after, *Sept.*, 451  
   tetany, *July*, 242  
 Gastroduodenostomy, lateral, for peptic ulcer, recurrence after, *Sept.*, 434  
 Gastro-enteroptosis, organic, *May*, 1808  
 Gastro-enterostomy for peptic ulcer, recurrent and anastomotic ulcer after, *Sept.*, 441  
 Gastro-intestinal manifestations of systemic disease and their differential diagnosis, *Jan.*, 1251-1263  
   motility, intestinal toxemia and, *May*, 1824  
   tract, absorption in, clinical factors, *March*, 1685-1693

- Gastro-intestinal tract in development of deficiency diseases, *Sept.*, 468
- Gastrojejunal ulcer following gastro-enterostomy, *Sept.*, 442
- Gastrojejuno-colic fistula, anemia with, *July*, 67
- Gastropsis, *May*, 1807
- Gastrotomy, anemia following, *July*, 67
- Gentian violet treatment of burns, *May*, 1944
- Giant-cell tumor of bone, roentgen treatment, *Sept.*, 601
- Giardia intestinalis in bile, *Nov.*, 680
- Gifford's sign, *Jan.*, 1208
- Ginger paralysis, *Nov.*, 953
- Glaucoma, headache in, *Jan.*, 1203
- Glénard's disease, *May*, 1808
- Glomerulonephritis in scarlet fever, treatment, *March*, 1396
- Glossitis, atrophic, nutritional factors, *July*, 59
- Glossopharyngeal neuralgia, relief of, *Jan.*, 1028
- Glucose administration, *May*, 1853
- Goiter, adenomatous, diffuse, *May*, 1718
- adolescent, *May*, 1717, 1718
- endemic, prevention and treatment, *May*, 1715-1724
- exophthalmic, eye symptoms, *Jan.*, 1204
- in pregnancy, prevention, *May*, 1716
- intrathoracic, *May*, 1722
- malignant, *May*, 1755, 1773
- radiotherapy, *May*, 1779
- nontoxic, effects of irradiation, *May*, 1768
- pathology, *May*, 1766
- toxic, pathology, *May*, 1766
- radium therapy, *May*, 1771
- roentgen therapy, *May*, 1770
- treatment, *March*, 1377
- Gonadal insufficiencies, pituitary, *Nov.*, 832
- Gonococcal arthritis, treatment, *Sept.*, 551-559, 589; *March*, 1368-1370
- urethritis, fever therapy, *Sept.*, 588
- Gonorrhea in women, *Nov.*, 911-914
- treatment, *Nov.*, 914-926
- Gonorrheal vulvovaginitis in children, *March*, 1445; *May*, 1999-2004
- Gout, dietary treatment, *May*, 1839
- postoperative, acute, identification of, *Sept.*, 560-566
- prevention and treatment, *Sept.*, 566-573; *March*, 1375
- Gradenigo's syndrome, *Jan.*, 1046
- Graham test in gallbladder disease, errors in interpretation, *Nov.*, 678
- Grand mal, *July*, 260
- Granulocytoclastic crisis, *July*, 115
- Granulomata of ear, *Jan.*, 1054
- Graves' disease, eye symptoms, *Jan.*, 1204
- Growth in children, *July*, 307-317
- Gynecological lesions, pain in, *Jan.*, 1122, 1131
- Gynecology, medical, recent advances, *March*, 1439-1466
- HALLUX rigidus, *Jan.*, 1074
- Hartmann's solution in diabetic coma, *Nov.*, 803
- Hashimoto's struma, *May*, 1761
- Hay fever, diagnosis and treatment, *March*, 1467-1492, 1547-1562; *May*, 1915-1930
- Head injuries, eye symptoms, *Jan.*, 1238
- Headache due to migraine, relief of, *Jan.*, 1015
- eyestrain and, *Jan.*, 1202
- in brain tumor, *Jan.*, 1203
- in glaucoma, *Jan.*, 1203
- menopausal, *July*, 217
- pituitary, *Nov.*, 833
- waking, *Jan.*, 1202
- Heart block, convulsions and unconsciousness in, *July*, 243
- frequency, *July*, 123-129
- treatment, *July*, 129-131
- disease, crises of, emergency management, *May*, 1857-1864
- gastro-intestinal manifestations, *Jan.*, 1261
- hyperthyroidism simulating, *May*, 1734
- in pregnancy, management. *Nov.*, 893-899
- organic, masking hyperthyroidism, *May*, 1740
- neurocirculatory asthenia complicating, *March*, 1543
- treatment, recent advances, *March*, 1321-1341
- with hyperthyroidism, management, *May*, 1725
- disorderly action, *March*, 1534
- failure complicating chronic glomerular nephritis, *July*, 171
- congestive, management, *March*, 1563-1570
- emergency, *May*, 1857
- involvement in diphtheria, *Nov.*, 737
- murmurs, significance and interpretation, *March*, 1505-1518
- pain in region of, *March*, 1533-1545
- soldier's, *March*, 1534
- Heat rash, *May*, 1879, 1880

- Hegar's sign, *March*, 1661  
Hemolytic crisis, acute, *Sept.*, 548, 549  
jaundice, *Sept.*, 545, 549  
Hemophilia, *May*, 1974, 1981  
Hemoptysis in pulmonary tuberculosis, management, *Nov.*, 901-904  
Hemorrhage of newborn, *May*, 1974  
transfusions in, *May*, 1977, 1980  
Hepatitis, biliary drainage in, therapeutic value, *Nov.*, 687  
Hernia, diaphragmatic, anginal pain in, *Jan.*, 1083  
Herpes zoster of auricle, *Jan.*, 1052  
Hexuronic acid, *Sept.*, 482  
Hilar nodes, tuberculous, *Nov.*, 711  
Hirsutism, *March*, 1442  
Histamine in arterial hypertension, *March*, 1349  
Hodgkin's disease, abdominal, *Sept.*, 423-427  
itching in, treatment, *Nov.*, 967-970  
Homosexuality, *Nov.*, 938  
Hormone therapy, female, *March*, 1462  
in Addison's disease, *Sept.*, 392-396  
in amenorrhea, *March*, 1453  
in arterial hypertension, *March*, 1353  
in breast conditions, *March*, 1451  
in dysmenorrhea, *March*, 1456  
in functional metrorrhagia, *Sept.*, 361; *March*, 1459  
in gonorrheal vulvovaginitis in children, *May*, 2001  
in menopause, *July*, 220, 221; *March*, 1462  
in pituitary disorders, *Nov.*, 818  
in prostatic hypertrophy, *May*, 1949-1957  
in pruritus vulvae, *May*, 1910  
in secondary anemia, *July*, 100  
in sterility, *March*, 1449  
Hormones, urine tests for, *March*, 1440  
Hunt's zoster auriculæ, *Jan.*, 1052  
Huntton's antibody solution in pneumonia, *July*, 6  
Hydroa vacciniforme, *May*, 1877  
Hydrocephalus, convulsions due to, *July*, 251, 254  
Hydromyelia, *March*, 1577  
Hydronephrosis, nocturnal pain in, *May*, 1800  
Hydrosalpinx, gonorrheal, *Nov.*, 920  
Hyperinsulinism, *July*, 233  
Hypersensitiveness, tests for, *March*, 1471  
Hypertension, *July*, 133  
arteriosclerosis with, *July*, 139  
cold test in, *Sept.*, 518  
Hypertension complicating chronic glomerular nephritis, *July*, 171  
essential, *Sept.*, 517-524  
diagnosis and treatment, *May*, 1865  
familial, *July*, 137; *Sept.*, 517  
surgery in, *Sept.*, 522; *March*, 1354  
latent, *Sept.*, 521  
malignant, *July*, 134  
masking hyperthyroidism, *May*, 1740  
menopausal, *July*, 216  
treatment, *July*, 133-149; *March*, 1343-1365  
Hypertensive encephalopathy, *July*, 238  
Hypertherm, Kettering, *Sept.*, 585  
Hyperthyroidism, *May*, 1719, 1722  
apathetic, *May*, 1736  
atypical, *May*, 1733-1742  
complications, management, *May*, 1725-1732  
divided operation, care between stages, *May*, 1787  
emaciation in, treatment, *May*, 1853  
gastro-intestinal manifestations, *Jan.*, 1258  
postoperative complications, prevention, *May*, 1790  
treatment, *May*, 1785  
preoperative treatment, *May*, 1783  
prognosis, unfavorable, signs, *May*, 1788  
Hyperventilation tetany, *July*, 242  
Hypochromic anemia, idiopathic, *July*, 69  
Hypoglycemia, *July*, 233  
chronic, causes and treatment, *May*, 2005-2020  
convulsions of, *July*, 234  
Hypogonadism, pituitary, *Nov.*, 828  
Hypoparathyroid tetany, *July*, 242, 243  
Hypotension, *Nov.*, 865-871  
Hypothyroidism, diagnosis and treatment, *May*, 1743-1753  
in childhood, *May*, 1717  
Hysterectomy, carcinoma of cervical stump following, *Sept.*, 352  
Hysteria, traumatic, *Nov.*, 838, 839  
Hysterical convulsions, *July*, 245  
in children, *July*, 260  
ICTERUS index, *Jan.*, 1166  
Id eruption of scalp, *Jan.*, 1248  
Ileitis, regional, *Sept.*, 413  
Ileostomy in ulcerative colitis in children, *March*, 1680  
Ileum, ulcers of, *Sept.*, 380

- Ileus, *Sept.*, 377
- Illumination tests of eye, *Jan.*, 1195, 1197
- Immunity in newborn, *Nov.*, 733
- Immunization against infectious diseases of childhood, *Nov.*, 731-744; *Jan.*, 1277-1290
- Impetigo contagiosa, *March*, 1627 of newborn, *March*, 1630
- Indigestion, acute, anginal pain in, *Jan.*, 1083  
in children, *March*, 1609  
nocturnal, diagnosis and treatment, *May*, 1797-1806
- Infant feeding, difficult cases, *Nov.*, 785-789
- Infantile paralysis. See *Polio-myelitis*.
- Infantilism, pituitary, *Nov.*, 825, 826
- Infections, acute, in infants, convulsions due to, *July*, 251, 252  
resistance to, vitamins and, *Sept.*, 471  
roentgen treatment, *Sept.*, 597
- Infectious diseases of childhood, immunization against, *Nov.*, 731-744; *Jan.*, 1277-1290
- Inflammatory conditions, roentgen treatment, *Sept.*, 597  
disease, pelvic, gonorrheal, *Nov.*, 920
- Inflations in otitis media, *Jan.*, 1042
- Influenzal meningitis, *Nov.*, 768
- Inhibin, *May*, 1950
- Insect bites, skin eruptions from, *May*, 1882-1884
- Insomnia in hypertension, treatment, *July*, 144  
menopausal, *July*, 218  
treatment, *March*, 1597-1601
- Insulin in diabetes of childhood, *July*, 277; *Nov.*, 791-805  
in nondiabetic malnutrition, *May*, 1854
- Intercourse, unsatisfactory, treatment of, *July*, 267
- Intertrigo, *May*, 1880, 1881
- Intestinal absorption, clinical factors, *March*, 1685  
anastomosis, multiple, macrocytic anemia following, *July*, 67  
obstruction in children, *March*, 1606  
toxemia, *May*, 1819-1830
- Intestine, small, lesions of, other than peptic ulcer, *Sept.*, 365-382
- Intracranial disease, abdominal pain in, *March*, 1614  
psychopathic personality and, *May*, 1994  
vertigo in, *March*, 1620
- Intradermal skin test, *March*, 1473, 1554; *May*, 1920
- Intranasal test for allergens, *May*, 1921
- Intrathoracic goiter, *May*, 1722
- Intussusception, *Sept.*, 378; *March*, 1605
- Iodine deficiency in pregnancy, *May*, 1716  
in production of thyroid disease, *May*, 1723  
in puberty and adolescence, *May*, 1717  
test for carcinoma of cervix, *March*, 1443
- Iron therapy in secondary anemias, *July*, 93-96
- Irradiation. See *Roentgen* and *Radium*.
- Irritable colon, *Jan.*, 1123, 1127; *March*, 1608; *May*, 1804
- Itching, *Nov.*, 971-980  
in Hodgkin's disease, treatment, *Nov.*, 967-970  
of vulva, *March*, 1445, 1446; *May*, 1893-1913  
treatment, *Nov.*, 980-987
- Ivy dermatitis, *May*, 1885-1889
- JACKSONIAN convulsions, *July*, 260
- Jacquet's dermatitis, *May*, 1881
- Jaeger's test types, *Jan.*, 1193
- Jake paralysis, *Nov.*, 953
- Jaundice, catarrhal, biliary drainage in, therapeutic value, *Nov.*, 685  
diagnosis and medical management, *Jan.*, 1163  
four clinical types arising from atypical blood dyscrasia, *Sept.*, 545-550  
hemolytic, *Sept.*, 545-549  
in abdominal Hodgkin's disease, *Sept.*, 425  
in cholelithiasis, *Nov.*, 644  
inactivation of chronic infectious arthritis and fibrositis by, *Sept.*, 573-583  
with hepatic insufficiency, treatment, *March*, 1651-1657
- Jejunal ulcer following gastro-enterostomy, *Sept.*, 442
- Joints, diseases of, *Sept.*, 551-583
- Juvenile diabetes, *July*, 273-286
- KARELL diet, *July*, 174
- Kerion of scalp, *Jan.*, 1247, 1248; *March*, 1635
- Ketogenic diet in epilepsy, *July*, 263
- Kettering hypertherm, *Sept.*, 585
- Kidney, carcinoma of, roentgen treatment, *Sept.*, 601

- Kidney, denervation, for hypertension, *March*, 1359  
 disorders, gastro-intestinal manifestations, *Jan.*, 1262  
 in pregnancy, prevention, *July*, 295-299  
 Koerner's syndrome, *Jan.*, 1052  
 Kolmer's serum in poliomyelitis prophylaxis, *Nov.*, 742; *Jan.*, 1290  
 Kramm's approach to parapharyngeal abscess, *Jan.*, 1159  
 Kraurosis vulvae, *March*, 1446; *May*, 1900, 1910  
 Krueger's pertussis vaccine, *Nov.*, 738, 739; *March*, 1415
- LACERATIONS of cervix, *Sept.*, 348  
*Lambia* intestinalis in bile, *Nov.*, 680  
 Laryngeal neuralgia, superior, relief of, *Jan.*, 1029  
 Laryngitis, earache in, *Jan.*, 1055  
 Lavage, gastric, for diagnosis of tuberculosis, *Nov.*, 721  
 Lead neuritis, *Nov.*, 953  
 poisoning, abdominal pain in, *March*, 1613  
 in children, convulsions from, *July*, 257  
 Lentilles, *May*, 1876  
 Leprous polyneuritis, *Nov.*, 958  
 Leukemia, chronic myelogenous, *Sept.*, 546, 549  
 in children, *May*, 1971  
 Leukopenia, pernicious, *July*, 103-122  
 Leukoplakic vulvitis, *March*, 1446; *May*, 1900, 1910  
 Leukorrhea, *Sept.*, 349  
 Lichen planus of vulva, *May*, 1899, 1909  
 Lipemia, retinal, *Jan.*, 1233  
 Liver, active principle, *July*, 49, 75  
 storage of, *July*, 57, 58  
 disease in children, pain in, *March*, 1611  
 extract, intra-osseous injection, in pernicious anemia, *July*, 50  
 extrinsic factor, *July*, 49, 51  
 functional tests, *Jan.*, 1165  
 insufficiency, with jaundice, treatment, *March*, 1651-1657  
 therapy in secondary anemias, *July*, 96  
 Liver-stomach mixtures in pernicious anemia, *July*, 49  
 Lobar pneumonia. See *Pneumonia*.  
 Lobectomy for bronchiectasis, *Jan.*, 1175  
 Löwenstein's culture medium in tuberculosis, *Nov.*, 722  
 Lumbago, relief of, *Jan.*, 1033-1038
- Lumbar puncture in pseudo-uremic convulsions, *July*, 240  
 Luminal. See *Phenobarbital*.  
 Lung, abscess of, bronchial obstruction in, *Sept.*, 456, 462  
 complicating pneumonia, *July*, 33, 34  
 carcinoma of, bronchial obstruction in, *Sept.*, 456  
 tuberculosis of. See *Tuberculosis, pulmonary*.  
 Lupus erythematosus, *May*, 1877, 1878  
 of scalp, *Jan.*, 1242  
 visceral lesions of, *July*, 333-346  
 miliaris disseminatus faciei, *Sept.*, 617  
 Lyon's test in gallbladder disease, diagnostic value, *Nov.*, 679
- MACULA lutea, *Jan.*, 1200  
 Malarial treatment of rheumatoid arthritis, *March*, 1372  
 Malignant hypertension, *July*, 134  
 tumors, roentgen treatment, *Sept.*, 598-603  
 Malnutrition, treatment, *May*, 1849-1855  
 Mantoux tuberculin test, *Nov.*, 703  
 March foot, *Jan.*, 1075  
 Marmite in pernicious anemia, *July*, 52, 54, 55, 56, 73  
 Marschik's approach to parapharyngeal abscess, *Jan.*, 1158  
 Massage, prostatic, *Jan.*, 1181, 1184  
 Mastoiditis, pain of, relief, *Jan.*, 1044-1047  
 Maxillary sinus infection, pain in, *Jan.*, 1062  
 McBurney's point symptoms in appendicitis, *July*, 190  
 McKhann's placental extract, *March*, 1417  
 Measles, immunization, *Nov.*, 734, 735; *Jan.*, 1287; *March*, 1417  
 Meckel's diverticulum, *Sept.*, 372, 373  
 Mediastinitis, pain in, simulating coronary disease, *Jan.*, 1079  
 Memory impairment, menopausal, *July*, 217  
 Ménière's syndrome, *March*, 1619  
 Meningitis, *Nov.*, 751-769  
 Meningococcus antitoxin, *March*, 1423  
 Menopause, symptoms and treatment, *July*, 205-226; *March*, 1462  
 masking hyperthyroidism, *May*, 1740  
 Menorrhagia, menopausal, *July*, 214  
 Menstruation, delayed, *March*, 1453

- Mental attitude in inoperable cancer, *July*, 196  
 disorders, puerperal, *Nov.*, 927-941  
 Mercupurin in heart disease, *March*, 1329  
 Mercury polyneuritis, *Nov.*, 955  
 Mersalyl in heart disease, *March*, 1329  
 Metabolic disturbances in gallbladder disease, *Nov.*, 664  
   of pituitary gland, *Nov.*, 832  
 Metropathia hemorrhagica, *March*, 1460  
 Metrorrhagia, functional, *Sept.*, 359-364; *March*, 1459  
 Middle ear disease, pain in, *Jan.*, 1041  
 Migraine, relief of, *Jan.*, 1015  
 Miliaria crystalline, *May*, 1879, 1880  
 Miliary tuberculosis, roentgen findings, *Nov.*, 712  
 Milk, evaporated, for infants, *Nov.*, 787  
 Mitral stenosis, murmurs of, *March*, 1514  
   systolic murmur, *March*, 1507  
 Moebius' sign, *Jan.*, 1208  
 Molimina, *March*, 1442  
 Monilia vaginitis, *March*, 1445  
 Moro tuberculin test, *Nov.*, 703  
 Mosher's approach to parapharyngeal abscess, *Jan.*, 1158  
 Moth, dermatitis due to, *May*, 1883  
 Motor education, corrective, in birth injuries, etc., *Nov.*, 800-815  
 Mouth care in pneumonia, *July*, 16  
 Mucous colitis, *Jan.*, 1123, 1128  
   membrane of mouth, atrophy of, *July*, 59  
 Mumps, *Nov.*, 736  
   immunization, *Jan.*, 1290  
 Murmurs, heart, significance and interpretation, *March*, 1505-1518  
 Myocardial failure following thyroidectomy, prevention, *May*, 1794  
   with hyperthyroidism, *May*, 1726  
 Myoma of small intestine, *Sept.*, 371  
 Myringotomy, *Jan.*, 1042
- NABOTHIAN cysts, *Sept.*, 349  
 Nail, ringworm of, *March*, 1648  
 Nausea in acute appendicitis, *July*, 186, 193  
   in inoperable cancer, treatment, *July*, 200  
 Neck, venous hum in, *March*, 1517  
 Neosynthalin as insulin substitute, *Nov.*, 803  
 Nephritis, chronic glomerular, complicated, *July*, 171-176  
 Nephritis, eye symptoms, *Jan.*, 1235  
   in scarlet fever, treatment, *March*, 1396  
 Nephroptosis, *May*, 1807  
 Nephrosis, amyloid, proteosuria in, *July*, 177-184  
   complicating chronic glomerular nephritis, *July*, 171  
 Nervous system, intestinal toxemia and, *May*, 1823  
   syphilis of, fever therapy, *Sept.*, 590  
   vegetative, rôle in climacteric, *July*, 210  
 Neufeld reaction for pneumococcus types, Sabin's technic, *July*, 3, 4  
 Neuralgia, dental causes, *Jan.*, 1063  
   glossopharyngeal, relief of, *Jan.*, 1028  
   laryngeal, superior, relief of, *Jan.*, 1029  
   occipital, relief of, *Jan.*, 1030  
   Sluder's, relief of, *Jan.*, 1031  
   trigeminal, relief of, *Jan.*, 1017-1028  
 Neurasthenia, traumatic, *Nov.*, 838, 839  
 Neurectomy, retrogasserian, for trigeminal neuralgia, *Jan.*, 1028  
 Neuritis, multiple. See *Polynneuritis*.  
   optic, in brain abscess, *Jan.*, 1215  
 Neurocirculatory asthenia, *March*, 1534-1545  
   masking hyperthyroidism, *May*, 1739  
 Neurodermatitis, circumscribed, of vulva, *May*, 1901, 1909  
 Neurological manifestations of pernicious anemia, with treatment, *July*, 79-89  
 Neuromuscular disease, hyperthyroidism simulating, *May*, 1735  
 Neuropsychoses, menopausal, *July*, 216  
   puerperal, *Nov.*, 927-941  
 Neurosis, cardiac, *March*, 1533  
   vertigo due to, *March*, 1620  
 Nevi, spider, *Sept.*, 536  
 Newborn, hemorrhage of, *May*, 1974  
   immunity in, *Nov.*, 733  
 Night blindness in gastro-intestinal affections, *Sept.*, 468, 469  
 Nipple, bleeding, *March*, 1452  
 Nitrites in arterial hypertension, *March*, 1347  
 Nitroglycerin in angina pectoris, *Nov.*, 882, 883; *Jan.*, 1099  
 Nocturnal indigestion, diagnosis and treatment, *May*, 1797-1806  
 Nona, eye symptoms, *Jan.*, 1228  
 Nutritional anemia, *July*, 37-77

- OBESITY, pituitary, *Nov.*, 827, 832  
 Occipital neuralgia, relief, *Jan.*, 1030  
 Ocular vertigo, *March*, 1619  
 Onychomycosis, *March*, 1648  
 Ophthalmic disorders in hyperthyroidism, *May*, 1736  
   test for allergens, *May*, 1921  
 Ophthalmoplegia in epidemic encephalitis, *Jan.*, 1228  
 Ophthalmoscopic test, *Jan.*, 1198  
 Optic disk, *Jan.*, 1200  
   neuritis in brain abscess, *Jan.*, 1215  
 Organotherapy in pituitary disorders, *Nov.*, 818  
 Osteo-arthritis of spine, pain of, simulating angina pectoris, *Jan.*, 1077  
 Otagia, *Jan.*, 1039  
 Otitis media in scarlet fever, *March*, 1391  
   treatment, *March*, 1395  
   pain in, relief, *Jan.*, 1041-1048  
 Otodynia, *Jan.*, 1039  
 Otomycosis, *Jan.*, 1050  
 Ovarian factor in menopause, *July*, 205  
   hormones in arterial hypertension, *March*, 1353  
   urine tests for, *March*, 1440  
 Ovarian-pituitary interrelationship, *July*, 206  
 Ovulation, *March*, 1447  
 Oxygen therapy in congestive heart failure, *March*, 1565  
   in pneumonia, *July*, 9-12  
 Oxyuris vermicularis infestation of vulva, *May*, 1897, 1909
- PAIN, abdominal, clinical significance and relief, *Jan.*, 1113-1129  
   in children, *March*, 1603-1615  
   severe, following emotional storm, *Sept.*, 399-402  
   in acute appendicitis, *July*, 186, 190  
   in cystitis, *May*, 1959  
   in dental field, *Jan.*, 1057-1066  
   in inoperable cancer, control, *July*, 198  
   in pelvic lesions of female, relief, *Jan.*, 1122, 1131  
   in peptic ulcer, *Jan.*, 1120, 1126  
   in pneumonia, treatment, *July*, 13  
   in region of heart, *March*, 1533-1545  
   relief of, symposium on, *Jan.*, 1013  
   shoulder, in gallbladder disease, *Nov.*, 651  
   simulating pain of coronary disease, *Jan.*, 1070-1083  
 Painful feet, relief of, *Jan.*, 1060-1075
- Palpitation, menopausal, *July*, 216  
 Pancreas, disease of, associated with gallbladder disease, *Nov.*, 664  
 Pancreatic ferments, *Nov.*, 683  
 Paracentesis, abdominal, in congestive failure, *March*, 1570  
   of ear drum, *Jan.*, 1042  
 Paraldehyde as soporific, *March*, 1599  
 Paralysis, birth, corrective motor education, *Nov.*, 807-815  
   infantile. See *Poliomyelitis*.  
   jake or ginger, *Nov.*, 953  
 Parapharyngeal space infections, *Jan.*, 1152  
 Parasites in bile, *Nov.*, 680  
 Parental serum in measles, *Nov.*, 735  
 Paresthesia, menopausal, *July*, 217  
 Paronychia, chronic, *March*, 1647  
 Paroxysmal tachycardia, *Nov.*, 857-863; *March*, 1325  
   emergency treatment, *May*, 1863  
 Parry's disease, eye symptoms, *Jan.*, 1204  
 Passive transfer test for allergy, *May*, 1920, 1936  
 Patch test in eczema, *July*, 323  
 Pediculi, itching due to, *Nov.*, 976  
 Pellagra, *July*, 60-62; *March*, 1496  
   in gastro-intestinal disease or abnormality, *Sept.*, 468, 470  
   vitamin deficiency in, *Sept.*, 478  
 Pelvic abscess, gonorrheal, *Nov.*, 921  
   inflammatory disease, gonorrheal, *Nov.*, 920  
   lesions in female, pain of, relief, *Jan.*, 1122, 1131  
   sympathectomy, *Jan.*, 1136  
 Pelvimetry, prenatal, *March*, 1661  
 Peptic ulcer in children, *March*, 1608  
   nocturnal pain in, *May*, 1798  
   obstructive, diagnosis and management, *March*, 1519-1524  
   pain in, *Jan.*, 1120, 1126  
   perforation of, pain in, simulating coronary disease, *Jan.*, 1082  
   recurrent, reactivated and anastomotic, *Sept.*, 429-452  
 Periapical infection, pain in, *Jan.*, 1059  
 Pericardial effusion, emergency treatment, *May*, 1862  
   friction rubs, *March*, 1516  
 Pericarditis, acute fibrinous, simulating coronary disease, *Jan.*, 1078  
   complicating chronic glomerular nephritis, *July*, 171  
   constrictive, chronic, *March*, 1336  
   uremic, *July*, 238  
 Perichondritis, auricular, *Jan.*, 1051  
 Peritoneal puncture in pneumococcus peritonitis, *Nov.*, 851, 852

- Peritonitis in children, *March*, 1612  
 pneumococcus, *Nov.*, 847, 855  
 peritoneal puncture in, *Nov.*, 851, 852  
 postoperative, vaccination against, *Sept.*, 620
- Pernicious anemia. See *Anemia, pernicious*.  
 leukopenia, *July*, 103-122  
 Peroneal sign in tetany, *July*, 255
- Personality, psychopathic, *May*, 1985-1997
- Pertussis. See *Whooping cough*.
- Petit mal, *July*, 260
- Petroff's stool examination in tuberculosis, *Nov.*, 721
- Pharyngomaxillary space infections, *Jan.*, 1152
- Phenobarbital in angina pectoris, *Jan.*, 1104  
 in epilepsy, *July*, 262; *March*, 1594
- Phenolphthalein eruption of vulva, *May*, 1898
- Phrenicectomy for bronchiectasis, *Jan.*, 1175
- Phyone, *Nov.*, 818
- Physiotherapy in splachnoptosis, *May*, 1814
- Pick's disease, *March*, 1339
- Picrotoxin poisoning, convulsions in, *July*, 245
- Pigmentation in Addison's disease, *Sept.*, 387
- Pink disease, *Nov.*, 957
- Pinworms of vulva, *May*, 1897, 1909
- Pitocin, *Nov.*, 819
- Pitressin, *Nov.*, 819
- Pituitary disorders, classification, *Nov.*, 821  
 eye symptoms, *Jan.*, 1239  
 masking hyperthyroidism, *May*, 1741  
 treatment, *Nov.*, 817-835  
 extract, *Nov.*, 818  
 in Addison's disease, *Sept.*, 395  
 factor in menopause, *July*, 206  
 hormones, urine tests for, *March*, 1440  
 relationship to hypertension, *March*, 1355  
 solution, *Nov.*, 819
- Pituitary-ovarian interrelationship, *July*, 206
- Pituitrin, *Nov.*, 819
- Placental extracts in measles, *Nov.*, 734; *Jan.*, 1288; *March*, 1417
- Pleural effusion in pulmonary tuberculosis, rapid development, *Nov.*, 907
- Pleurisy, diaphragmatic, abdominal pain in, *Jan.*, 1115
- Pleurisy, fibrinous, pain in, simulating coronary disease, *Jan.*, 1081
- Plummer-Vinson's syndrome, *July*, 71
- Pneumococcus peritonitis, *Nov.*, 847-855  
 types, determining, *July*, 3, 4
- Pneumolysis, perforation of lung following, *Nov.*, 909
- Pneumonia, abdominal pain in, *Jan.*, 1115; *March*, 1613  
 artificial pneumothorax in, *July*, 19-27  
 digitalization in, *July*, 14  
 nursing care and diet in, *July*, 15-18  
 oxygen therapy, *July*, 9-12  
 pain in, simulating coronary disease, *Jan.*, 1081  
 postthyroidectomy, prevention, *May*, 1793  
 specific therapy, *July*, 3-9  
 surgical complications, *July*, 29-35  
 symptomatic treatment, *July*, 12-14
- Pneumothorax, artificial, air embolism during, *Nov.*, 908  
 in hemoptysis of pulmonary tuberculosis, *Nov.*, 904  
 in lobar pneumonia, *July*, 19-27  
 spontaneous, in pulmonary tuberculosis, treatment, *Nov.*, 904-907  
 pain in, simulating coronary disease, *Jan.*, 1080
- Poliomyelitis, acute anterior, immunization, *Jan.*, 1290  
 recent developments, *Nov.*, 740-744
- Politzer bag ear inflation, *Jan.*, 1042
- Pollen hay fever, *March*, 1467-1492, 1547-1562; *May*, 1915-1930
- Polyneuritis, *July*, 68; *Nov.*, 943  
 treatment, *Nov.*, 943-958  
 vitamin deficiency in, *Sept.*, 478, 481
- Post cautery in gonorrhea of cervix, *Nov.*, 915
- Postoperative arthritis, acute, identification of, *Sept.*, 560-566  
 prevention and treatment, *Sept.*, 566-573  
 gas pains, *Jan.*, 1125
- Postural exercises in splachnoptosis, *May*, 1815  
 hypotension, *Nov.*, 868
- Postvaccinal encephalitis, *Jan.*, 1280
- Potassium iodide in angina pectoris, *Jan.*, 1104  
 permanganate for ivy poisoning, *May*, 1886  
 thiocyanate in arterial hypertension, *March*, 1352
- Pregnancy, anemia of, *July*, 38, 65



- Pregnancy, goiter in, prevention, *May*, 1716  
   heart disease in, management, *Nov.*, 893-899  
   hyperthyroidism in, management, *May*, 1731  
   kidney disorders in, prevention, *July*, 295-299  
   polyneuritis, *Nov.*, 953  
   tests, *March*, 1452  
 Premenstrual feelings, *March*, 1442  
 Prenatal care in private practice, *March*, 1659-1671  
 Prickly heat, *May*, 1879, 1180  
 Prize fighter ear, *Jan.*, 1053  
 Proctitis, gonorrheal, *Nov.*, 921  
 Progesterin, *March*, 1463  
   in amenorrhea, *March*, 1454  
   in dysmenorrhea, *March*, 1457  
 Prolactin, *Nov.*, 819  
 Prolan, *Nov.*, 818; *March*, 1462  
   in functional bleeding, *March*, 1460, 1461  
   in urine, test, *March*, 1440  
 Proluton in functional metrorrhagia in young women, *Sept.*, 361  
 Prostate gland, rectal palpation, *Jan.*, 1181  
 Prostatic hypertrophy, benign, endocrine therapy, *May*, 1949-1957  
   massage, *Jan.*, 1181, 1184  
 Prostatitis, *Jan.*, 1181  
 Protein sensitization test, *March*, 1471  
 Proteosuria in amyloid nephrosis, *July*, 177-184  
 Pruritus, *Nov.*, 971-980  
   in Hodgkin's disease, *Sept.*, 426; *Nov.*, 967-970  
   treatment, *Nov.*, 980-987  
   vulvae, *March*, 1445; *May*, 1893-1905  
   treatment, *May*, 1905-1913  
 Pseudonarcotism at menopause, *July*, 218  
 Pseudo-uremia, *July*, 236, 238  
   convulsions of, *July*, 238-241  
 Psychic effect of abdominal trauma, *Nov.*, 837-845  
 Psychoanalysis in puerperal psychoses, *Nov.*, 941  
 Psychoneuroses with hyperthyroidism, *May*, 1730  
 Psychopathic personalities, constitutional, *May*, 1985-1997  
 Psychoses, menopausal, *July*, 216, 218  
   puerperal, *Nov.*, 927-941  
   with hyperthyroidism, management, *May*, 1730  
 Psychotherapy in splachnoptosis, *May*, 1813  
 Ptomaine poisoning, nocturnal indigestion in, *May*, 1804  
 Ptosis, abdominal, *May*, 1807  
 Puerperal polyneuritis, *Nov.*, 957  
   psychoses, *Nov.*, 927-941  
 Pulmonary. See also *Lungs*.  
   edema, acute, with cardiac asthma, *May*, 1861  
   embolism simulating coronary disease, *Jan.*, 1079  
   regurgitation, murmur in, *March*, 1515  
 Pulpitis, pain in, *Jan.*, 1057  
 Pupil tests, *Jan.*, 1196  
 Purin derivatives in congestive heart failure, *March*, 1569  
   in nephritis with vascular and cardiac complications, *July*, 175  
 Purpura hemorrhagica in scarlet fever, treatment, *March*, 1398  
   in children, *May*, 1974  
   abdominal pain in, *March*, 1612  
 Pyemia following tonsillar infections, treatment, *Jan.*, 1151  
 Pyloric stenosis, hypertrophic, congenital, *March*, 1604  
 Pyloroplasty for peptic ulcer, recurrence after, *Sept.*, 440  
 Pyodermias, staphylococcus toxoid in, *March*, 1431  
 Pyrexia in children, convulsions due to, *July*, 252  
 Pyuria in cystitis, *May*, 1959  
  
 QUINIDINE therapy in heart disease, *March*, 1322  
 Quinine in paroxysmal tachycardia, *Nov.*, 861  
   in pneumonia, *July*, 6  
  
 RABIES, immunization, *Jan.*, 1290  
 Radium treatment of functional metrorrhagia, *Sept.*, 363  
   of thyroid disease, *May*, 1765-1782  
 Ragweed dermatitis, *May*, 1889  
 Raynaud's disease, treatment, *July*, 148  
 Rectal feeding, *May*, 1852  
 Rectum, gonorrhea of, *Nov.*, 921  
 Renal colic, *Jan.*, 1119, 1124  
   nocturnal pain in, *May*, 1804  
 Resistance to infections, vitamins and, *Sept.*, 471  
 Respirator in poliomyelitis, *Nov.*, 743  
 Respiratory tract infections, abdominal pain in, *March*, 1613

- Rest in angina pectoris, *Jan.*, 1097  
in congestive heart failure, *March*, 1563  
in hypertension, *July*, 143  
in pneumonia, *July*, 15  
in splachnoptosis, *May*, 1813  
in tuberculosis, *July*, 228, 230  
Reticulocyte count in pernicious anemia, *July*, 40  
Retinal hemorrhages in diabetes, *Jan.*, 1234  
lipemia, *Jan.*, 1233  
vessels, examination, *Jan.*, 1201  
Retinitis, albuminuric, *Jan.*, 1236  
arteriosclerotic, *Jan.*, 1210  
diabetic, *Jan.*, 1232  
Rheumatic fever, abdominal pain in, *March*, 1613  
Rheumatism, gonorrheal, *Sept.*, 551  
Rheumatoid arthritis, diet in, 1840  
treatment, *March*, 1370-1375  
Rhinitis, purulent, in scarlet fever, treatment, *March*, 1395  
vasomotor, *March*, 1468, 1547  
Rhizotomy for essential hypertension, *Sept.*, 523  
Rhus antigen in ivy poisoning, *May*, 1886  
Ribs, fracture of, pain in, simulating coronary disease, *Jan.*, 1081  
Rickets, dietetic factor, *Jan.*, 1291-1304  
tetany due to, *July*, 255  
vitamin deficiency in, *Sept.*, 478, 483  
Riedel's struma, *May*, 1760  
radiotherapy, *May*, 1772  
Ringworm of beard, *March*, 1638  
of nail, *March*, 1648  
of scalp, *Jan.*, 1241-1250; *March*, 1635  
Roentgen diagnosis of tuberculosis in children, *Nov.*, 706-721  
epilation of scalp, *Jan.*, 1246; *March*, 1637, 1639  
treatment of inflammatory and malignant conditions, *Sept.*, 597-603  
of pruritus, *Nov.*, 983  
vulvae, *May*, 1910  
of syringomyelia, *March*, 1578  
of thyroid disease, *May*, 1765-1782  
Roseola infantum, abdominal pain in, *March*, 1613  
Rowe's elimination diets, [*March*, 1490  
Rupture of ear drum, traumatic, *Jan.*, 1054  
Rush method of desensitization, *March*, 1483  
SABIN's technic for Neufeld reaction for pneumococcus types, *July*, 3, 4  
Salpingitis, gonorrheal, *Nov.*, 919, 920  
fever therapy, *Sept.*, 588, 590  
Salt soaks in burns, *May*, 1945  
therapy in Addison's disease, *Sept.*, 391; *Nov.*, 959-965  
Salyrgan in congestive heart failure, *March*, 1569  
in heart disease, *March*, 1326  
Sarcoma of small intestine, *Sept.*, 370  
of thyroid gland, *May*, 1755, 1778  
Sauer's pertussis vaccine, *Nov.*, 738; *Jan.*, 1288; *March*, 1413  
Scalp, ringworm and related lesions of, *Jan.*, 1241-1250; *March*, 1635  
x-ray epilation, *Jan.*, 1246; *March*, 1637, 1639  
Scarlet fever, *Nov.*, 739  
complications, *March*, 1391  
treatment, *March*, 1395-1399  
Dick test, *Jan.*, 1285  
immunization, *Jan.*, 1285  
treatment, *March*, 1389-1395  
Schock test, *Jan.*, 1282  
School problems in diabetes, *July*, 282  
Sciatica, relief of, *Jan.*, 1033-1038  
Scratch test in hay fever, *March*, 1472  
*May*, 1920  
Scurvy, *March*, 1493  
vitamins and, *Sept.*, 478  
Seasickness, *March*, 1619  
Sedimentation test in tuberculosis in children, *Nov.*, 724  
Sensitization tests in hay fever, *March*, 1471, 1553; *May*, 1920  
Sepsis following tonsillar infections, treatment, *Jan.*, 1151  
transfusions in, *May*, 1980  
Septic sore throat, *Jan.*, 1143  
Serum prophylaxis of poliomyelitis, *Nov.*, 742; *Jan.*, 1290  
reaction in meningitis, *Nov.*, 766  
sickness from scarlet fever anti-toxin, *March*, 1393  
treatment of diphtheria, *March*, 1401  
of meningitis, *Nov.*, 760; *March*, 1423  
of pneumonia, *July*, 3-6  
of scarlet fever, *March*, 1389  
Serums, recent advances, *March*, 1409-1434  
Sex determination, *March*, 1448  
Sexual desire and hypertension, *July*, 146  
Shoulder pain in gallbladder disease, *Nov.*, 651  
Simmond's disease, *Nov.*, 825  
emaciation in, treatment, *May*, 1854



- eeth, unerupted and impacted, pain due to, *Jan.*, 1062  
 elangiectases, *Sept.*, 536  
 emporomandibular joint diseases, pain in, *Jan.*, 1065  
 ension of eye, testing, *Jan.*, 1195  
 est types, visual, *Jan.*, 1190  
 esticular hormone therapy in prostatic hypertrophy, *May*, 1949  
 estis, tumors of, roentgen treatment, *Sept.*, 599  
 estosterone, *May*, 1949  
 etanus, immunization, *Jan.*, 1284; *March*, 1420-1423  
 neonatorum, *July*, 251  
 etany, *July*, 241-243  
 infantile, *July*, 254  
 hallium acetate in tinea, *March*, 1638  
 neuritis, *Nov.*, 955  
 heelin in gonorrheal vulvovaginitis, *May*, 2001  
 heobromine in angina pectoris, *Jan.*, 1101  
 heophylline in angina pectoris, *Jan.*, 1101  
 heophylline - ethylene - diamine in heart disease, *March*, 1321  
 thiocyanate in arterial hypertension, *March*, 1351  
 throat, sore, septic, *Jan.*, 1143  
 thrombopenia in children, *May*, 1974  
 thrombophlebitis, *Sept.*, 539-543  
 thrombosis, coronary, angina pectoris and, differentiation, *Jan.*, 1085  
 treatment, *Nov.*, 873-880, 887  
 of aorta and its larger branches, *July*, 159-170  
 thyrocardiac, *May*, 1734  
 thyroid crisis, prevention, *May*, 1790  
 gland, adenoma, calcified, *May*, 1761  
 diffuse, *May*, 1718  
 discrete, *May*, 1720  
 hemorrhage into, *May*, 1761  
 malignant, *May*, 1756, 1774  
 carcinoma of, *May*, 1721, 1757, 1776, 1777  
 roentgen therapy, *Sept.*, 600  
 carcinoma-sarcoma, *May*, 1757, 1777  
 diseases, gastro-intestinal manifestations, *Jan.*, 1258  
 iodine deficiency in production, *May*, 1723  
 irradiation in, *May*, 1765-1782  
 symposium on, 1713  
 treatment, *March*, 1377-1387  
 inflammations, *May*, 1760  
 radiotherapy, *May*, 1772  
 malignancy of, *May*, 1773  
 clinical problems, *May*, 1755-1764  
 Thyroid gland, malignancy of, radiotherapy, *May*, 1772  
 sarcoma of, *May*, 1755, 1775  
 tuberculosis of, radiotherapy, *May*, 1772  
 Thyroidectomy, care before and after, *May*, 1783-1795  
 for adenomatous goiter, indications, *May*, 1719  
 for angina pectoris, *Jan.*, 1105; *March*, 1333  
 for congestive heart failure, *March*, 1570  
 management between stages, *May*, 1787  
 prevention of complications, *May*, 1790  
 Thyroiditis, radiotherapy, *May*, 1772  
 thyroid malignancy and, *May*, 1760  
 Tic douloureux, relief of, *Jan.*, 1017  
 Tinea barbae, *March*, 1638  
 capitis, *March*, 1635, 1636  
 circinata, *March*, 1639  
 favosa, *March*, 1636  
 sycosis, *March*, 1638  
 unguium, *March*, 1648  
 versicolor, *March*, 1645  
 Tinnitus, menopausal, *July*, 218  
 Tissue extracts in angina pectoris, *Jan.*, 1103  
 in arterial hypertension, *March*, 1348  
 Tobacco, use of, in angina pectoris, *Nov.*, 883; *Jan.*, 1099  
 Tongue, black, *July*, 59  
 burning, *Jan.*, 1065  
 Tonsillar infections, sepsis and pyemia after, treatment, *Jan.*, 1151  
 Toothache, *Jan.*, 1057  
 ear pain in, *Jan.*, 1055  
 Toxemia, intestinal, *May*, 1819-1830  
 Toxicoses, transfusions in, *May*, 1979  
 Toxoid, diphtheria, *Nov.*, 736; *Jan.*, 1281  
 staphylococcus, *March*, 1426  
 tetanus, *Jan.*, 1285; *March*, 1420  
 Trachea, obstruction of, clinical and bronchoscopic findings, *Sept.*, 453-462  
 Transfusions, blood, citrate method, *May*, 1981  
 from convalescents in scarlet fever, *March*, 1394  
 in functional metrorrhagia, *Sept.*, 362  
 in general medical practice, *May*, 1977-1983  
 in inoperable cancer, *July*, 202  
 in measles, *Jan.*, 1288  
 in secondary anemias, *July*, 99

- Trendelenburg's test in varicose veins, *Sept.*, 536
- Trichomoniasis, vaginal, *March*, 1443  
with pruritus vulvae, *May*, 1897, 1909
- Trichophytide, *March*, 1644
- Trigeminal neuralgia, relief of, *Jan.*, 1017-1028
- Tropical macrocytic anemia, *July*, 66
- Trousseau's sign in tetany, *July*, 242
- Tuberculin reaction, *Nov.*, 702-706
- Tuberculosis, cutaneous, hematogenous type, *Sept.*, 611-618  
miliary, roentgen findings, *Nov.*, 712  
of small intestine, *Sept.*, 379  
of suprarenal glands in Addison's disease, *Sept.*, 384  
of thyroid gland, radiotherapy, *May*, 1772  
pulmonary, abdominal pain in, *Jan.*, 1116  
bronchial obstruction in, *Sept.*, 456  
crises in, management, *Nov.*, 901-909  
gastro-intestinal manifestations, *Jan.*, 1258  
home treatment, *July*, 227-231  
in children, diagnosis, *Nov.*, 701-729  
with hyperthyroidism, *May*, 1731
- Tuberculous bronchopneumonia in children, *Nov.*, 717  
hilar nodes, *Nov.*, 711  
meningitis, *Nov.*, 758, 759  
peritonitis in children, *March*, 1612
- Tumors, abdominal, in children, pain in, *March*, 1611  
gynecological, of endocrine significance, *March*, 1446  
malignant, roentgen treatment, *Sept.*, 598-603  
of brain. See *Brain, tumors of.*  
of small intestine, *Sept.*, 366, 370  
of trachea, obstructive, *Sept.*, 454  
pituitary, *Nov.*, 832
- Typhoid fever, immunization, *Jan.*, 1284
- ULCER, gastroduodenal, following gastroenterostomy, *Sept.*, 442  
of ileum, *Sept.*, 380  
peptic. See *Peptic ulcer.*  
varicose, *Sept.*, 539
- Ulceration, uremic, *July*, 238
- Ulcerative colitis, chronic, management, *Sept.*, 403-407  
two carcinomas complicating, *Sept.*, 408-410
- Ulcerative colitis, idiopathic, in children, *March*, 1673-1683  
enterocolitis, regional, *Sept.*, 411-422
- Ultraviolet treatment of pruritus, *Nov.*, 983  
of secondary anemias, *July*, 98
- Unconsciousness in heart block, *July*, 243
- Urea frost, *July*, 237
- Uremia, *July*, 236-241  
convulsions in, *July*, 236  
in children, *July*, 258
- Uremic poisoning, treatment, *Jan.*, 1270
- Urethra, female, gonorrheal infection, *Nov.*, 912, 922  
gonorrheal stricture, *Nov.*, 925  
milking of, *Nov.*, 913
- Urethral caruncle, *Nov.*, 923
- Urethritis, gonococcal, fever therapy, *Sept.*, 588
- Urinary frequency in cystitis, *May*, 1959  
incontinence in children, *July*, 287-294  
tract diseases, gastro-intestinal manifestations, *Jan.*, 1253, 1255  
in children, abdominal pain in, *March*, 1611
- Urine examination in pregnancy, *March*, 1663  
tests for pituitary and ovarian hormones, *March*, 1440
- Uterine bleeding, functional, *Sept.*, 359-364; *March*, 1459  
menopausal, *July*, 214  
cervix. See *Cervix uteri.*
- Uterus, dilatation of, *March*, 1458  
measurement of, *March*, 1441
- VACCINA, generalized, *Jan.*, 1279
- Vaccine, Krueger's pertussis, *Nov.*, 738, 739; *March*, 1415  
poliomyelitis, *Nov.*, 742; *Jan.*, 1290  
prophylaxis of colds, *Nov.*, 749; *March*, 1503  
rabies, *Jan.*, 1290  
Sauer's pertussis, *Nov.*, 738; *Jan.*, 1288; *March*, 1413  
smallpox, *Jan.*, 1277  
treatment of hay fever and asthma, *March*, 1487  
of pneumonia, *July*, 6  
of rheumatoid arthritis, *March*, 1373  
typhoid fever, *Jan.*, 1284
- Vaccines, recent advances, *March* 1409-1434

- Vaginal complications in gonorrhea, *Nov.*, 919  
inflammations and discharges, *March*, 1443
- Vaginitis, gonorrheal, *Nov.*, 919; *March*, 1445; *May*, 1999  
trichomonas, *March*, 1443; *May*, 1897
- Valsalva ear inflation, *Jan.*, 1042
- Van den Bergh reaction, *Jan.*, 1166
- Varicose ulcers, *Sept.*, 539  
veins, *Sept.*, 535-538
- Vascular crises in hypertension, management, *July*, 133, 143
- Vasomotor rhinitis, *March*, 1468, 1547
- Vasovagal syncope, *March*, 1622
- Vegex in pernicious anemia, *July*, 56, 73, 74
- Veins, diseases of, *Sept.*, 535-543
- Venesection in congestive heart failure, *March*, 1570; *May*, 1859  
in pseudo-uremic convulsions, *July*, 240
- Venous hum in neck, *March*, 1517  
pressure, *Jan.*, 1273-1276
- Vertigo e vesica fellea laesa, *Nov.*, 653  
in gallbladder disease, *Nov.*, 652  
menopausal, *July*, 218  
significance and treatment, *March*, 1617-1621
- Vioosterol in hay fever and asthma, *March*, 1488
- Virus diseases, *Nov.*, 732
- Visceral lesions of lupus erythematosus, *July*, 333-346
- Visual tests, *Jan.*, 1190, 1193
- Vitamin B and pernicious anemia, *July*, 51, 74  
factor in colds, *Nov.*, 748  
therapy in secondary anemias, *July*, 97  
in splanchnoptosis, *May*, 1811
- Vitamins, *Sept.*, 463-476; *March*, 1494  
chemical nature, *Sept.*, 477-485
- Volvulus, *Sept.*, 378
- Vomiting, cyclic, food allergy in, *May*, 1931
- Vomiting in acute appendicitis, *July*, 186, 193  
in inoperable cancer, treatment, *July*, 200
- Von Graefe's sign, *Jan.*, 1207
- Vulva, circumscribed neurodermatitis, *May*, 1901, 1909  
contact dermatitis, *May*, 1898  
drug eruption, *May*, 1898  
fungus infectious, *May*, 1896, 1907  
itching, *March*, 1445, 1446; *May*, 1893-1913  
kraurosis of, *March*, 1446; *May*, 1900, 1910  
lichen planus, *May*, 1899, 1909  
pinworms of, *May*, 1897, 1909
- Vulvitis, leukoplakic, *March*, 1446; *May*, 1900, 1910
- Vulvovaginitis, gonorrheal, *Nov.*, 919  
in children, *March*, 1445; *May*, 1999-2004  
trichomoniasis, *March*, 1443; *May*, 1897, 1908
- WEAKNESS in inoperable cancer, treatment, *July*, 201
- Weight loss in hyperthyroidism, *May*, 1736
- Westphal's sign, *Nov.*, 652
- Whitfield's ointment, *May*, 1907
- Whooping cough, *Nov.*, 732  
vaccine prophylaxis and treatment, *Nov.*, 738, 739; *Jan.*, 1288; *March*, 1409-1417
- XERODERMA pigmentosum, *May*, 1877
- Xerophthalmia and vitamin deficiency, *Sept.*, 478
- YEASTS, autolyzed, in pernicious anemia, effects, *July*, 51, 57
- ZOSTER auriculæ, Hunt's, *Jan.*, 1052



